MILITARY NEED FOR RESEARCH AND DEVELOPMENT OF A MALARIA VACCINE

A thesis presented to the Faculty of the U.S. Army Command and General Staff College in partial fulfillment of the requirements for the degree

MASTER OF MILITARY ART AND SCIENCE

by

KENNETH E. SPENCER, SR., MAJ, USA
B.S., NCA&T State University, 1969

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This study examines a military need for research and development of a malaria vaccine from several aspects: (1) the documentation of the incidence of malaria and the resultant noneffectiveness time experienced by American soldiers during two general and two limited wars; (2) an evaluation of past and current antimalarial prevention and control measures to institute during combat operations in endemic areas; (3) a review of the United States interests in two areas and assessment of the malarial threat in those areas;

and (4) a comparison of the Army and the Navy malaria vaccine development programs.

The study reveals that the history of the United States Army is replete with soldier noneffectiveness time because of contracting malaria. (Even though malaria was recognized as a disease of military significance as early as the American Revolution, it was a major cause of disease casualties during the Vietnam War. The preponderance of malaria casualties are generated in forward combat units where major breakdowns in antimalarial prevention and control measures occur. Consequently, malaria has had an influence on the outcomes of several battles involving American forces, and has serious implications in future combat operations in malarial endemic areas.)

Currently, there is a worldwide resurgence of malaria due to resistance of the malarial parasite or Plasmodium to antimalarial drugs, and resistance of the mosquito vector or Anopheles to insecticides. These two factors exacerbate the malarial threat in future wars and pose formidable challenges to unit mission accomplishment in malarial endemic areas. Since antimalarial prevention and control measures have been only partially successful in past years, soldiers will need permanent antimalarial protection, prior to deployment, in future wars. Active immunization is the method of conferring permanent protection, but currently no active immunization for malaria exist. Consequently, the author concludes that there is an immediate military need for research and development of a malaria vaccine.

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Name of candidate MAJOR KENNETH E. SPENCER

Title of thesis MILITARY NEED FOR RESEARCH AND DEVELOPMENT OF A MALARIA VACCINE

Approved by:

Steven T. Hayne, Thesis Committee Chairman
Major Steven T. Hayne, M.D.

James E. Cantrell, Member, Graduate Faculty
Colonel James E. Cantrell, M.H.A.

Allen W. Jones, Member, Consulting Faculty
Colonel Allen W. Jones, Ph.D.

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The opinions and conclusions expressed herein are those of the student author and do not necessarily represent the views of the U.S. Army Command and General Staff College or any other governmental agency. (References to this study should include the foregoing statement.)

ABSTRACT

MILITARY NEED FOR RESEARCH AND DEVELOPMENT OF A MALARIA VACCINE, by Major Kenneth E. Spencer, USA, 114 pages.

This study examines a military need for research and development of a malaria vaccine from several aspects: (1) The documentation of the incidence of malaria and the resultant noneffectiveness time experienced by American soldiers during two general and two limited wars; (2) an evaluation of past and current antimalarial prevention and control measures to institute during combat operations in endemic areas; (3) a review of the United States interests in two areas and assessment of the malarial threat in those areas; and (4) a comparison of the Army and the Navy malaria vaccine development programs.

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INTRODUCTION

Statement Of The Problem

Diseases are a major cause of disability among combat soldiers during war. Since antiquity, diseases have been responsible for more lost man-days by soldiers than casualities resulting from enemy engagement. Early records verify many instances of battles being abandoned or lost because of tremendous loss of soldiers to diseases. In 2000 BC plague decimated the Egyptian and Hittite armies in Syria; pestilences resembling bubonic plague are referred to in the Bible; malaria stymied Hannibal's troops in Syracuse; and Napoleon was denied the conquest of Russia due to typhus fever which accompanied the cold weather.[1] Of the many diseases prevalent throughout the world, malaria ranks high on the list of diseases of military significance in the twentieth century.

Malaria was recorded as a military medical problem many years prior to its current cognition and was a major cause of ineffectiveness among soldiers from the Civil War to the Vietnam War. The number of man-days lost due to malaria disease has influenced the outcome of many combat missions. Malaria is defined and described as:

> ... a tropical disease characterized by high fever, severe chills, enlargement of the liver, and anemia. ... An attack of malaria usually begins with chills that become worse as fever begins to rise,

> 103-104°F (39.9°C) or even higher. A severe headache usually develops. The fever breaks and profuse sweating occurs. A single infection may be characterized by repeated bouts of chills, fever and sweating before the disease runs its course.[2]

Malaria may be transmitted to man by three modes. The first, and perhaps most important, is transmission by an infective female Anophelus mosquito. Of over 200 known species of Anophelus mosquitoes, ninety have been identified as transmitters of malaria. Measures established to control the Anophelus mosquito population are discussed in detail in this thesis. Malaria may also be transmitted by transfusing blood of infected persons or by use of contaminated syringes. Finally, malaria may result from congenital transmission.[3]

The infective agent for human malarias is a protozoan and it belongs to the species Plasmodium. The four species of Plasmodium that infect man with malaria are: Plasmodium falciparum - falciparum malaria or malignant tertian; Plasmodium vivax - malaria or benign tertian; Plasmodium malariae - malariae malaria or quartan; and Plasmodium ovale - ovale malaria. Plasmodium falciparum malaria is the most life-threatening to humans and may result in cerebral malaria, respiratory complications, malaria dysentery and blackwater fever.[4] Plasmodium vivax malaria is particularly significant because of the relapsing effect of the disease.

Significance Of The Problem

Malaria is a significant problem for the military both overseas and in the United States. Throughout history, soldiers contracting the disease have had significant impact on accomplishing the mission. The

impact is measured in relation to the noneffectiveness rate of the unit, which is one of the most significant indexes used for measuring the health of the Army. The noneffectiveness rate is represented as the average daily number of patients in hospital and quarters on an excused from duty basis per 1,000 assigned personnel during the period considered.[5] American forces have sustained high noneffectiveness rates because of malaria during the last four wars. It is untenable to assume that the high incidence rate of malaria will decline in future wars as the problem has been exacerbated. Many forms of the Plasmodium organism either are resistant or are becoming resistant to antimalarial drugs. Many species of Anopheles are resistant to dichlorodiphenyltrichloroethane (DDT) which precludes them from being eradicated. The U.S. military will continue to have worldwide deployment missions in support of our national policies, and therefore, soldiers will continue to be vulnerable to noneffectiveness from lost man-days due to the malarial parasite.

In addition to malaria being significant to the military overseas, soldiers contracting the disease pose a malarial threat to the United States. As soldiers return to the United States from malaria endemic areas, they discontinue following their antimalaria regimen. As a result, both returning soldiers and the local populace are susceptible to contracting malaria. Increases in the number of cases of malaria in the United States occurred during engagements in the last three wars. The number of cases of malaria treated in Army facilities in the United States rose from 62 in 1965 to 2,222 in 1970, resulting from soldiers

returning from Vietnam.[6]

Thesis Hypothesis

Does the military have a need for research and development of a malaria vaccine? The primary focus of this thesis is to demonstrate the apparent failure of established control measures to eradicate both the anopheles mosquito and the Plasmodium organism. As a result, malaria remains a disease of significant military importance to demand a malarial vaccine.

Purpose Of The Study

The purpose of this thesis is to examine the military need for research and development of a malaria vaccine. This is accomplished by using several different methods which are designed to complement each other. First, past and present malaria preventine measures are assessed. Second, morbidity and mortality experienced by soldiers in two general and two limited wars are documented. Third, the potential effects of malaria on future military operations in two areas of interest to the United States are discussed. An attempt is made to correlate these data resulting in the military need for research and development of malaria vaccine. Finally, an assessment is made of current military malaria vaccine development programs.

Background Of The Problem

The word malaria has only been in existence since the 18th century, but its devastating effects on warring armies existed in biblical times. Italians dying of the intermittent fever were said to be

victims of bad air or mal' aria.[7] Malaria became incorporated into the English language about 1900.[8]

Malaria has been recognized as a major American military medical problem since the American Revolution. The consequence of contracting the disease has had devastating effects on soldiers during subsequent wars, to include the Vietnam War. During wars prior to 1900, military physicians treated diseased patients without sufficient scientific knowledge of those diseases. Doctors were not aware of microorganisms as causative agents of communicable diseases, insects as vectors to spread the diseases, intermediate host to harbor the organisms and carriers of infective hosts.[9] After discovery of microorganisms as causative agents and insects as vectors to transmit disease in the last quarter of the 19th century, emphasis was placed upon measures to control them.

Since malaria has been a disease of military interest to all armies, military physicians have contributed significantly to our current knowledge of the disease. The malarial parasite was first described by Charles Laveran, a French medical officer, while he was serving in Algiers in 1880.[10] In 1897, Ronald Ross, Indian medical officer, discovered plasmodium in the stomach wall of a mosquito which confirmed the mosquito as the vector of malaria.[11] These discoveries led to a two-prong approach to prevention of malaria. This approach called for the destruction of both the vector mosquito and the disease-causing parasite.

The general concept that insects were involved in the transmission of diseases was suspected prior to the 19th century. In 1854 the Bureau of Entomology, U.S. Department of Agriculture, was instructed to help

eradicate insect pests that were destroying crops.[12] This was followed by the establishment of numerous agencies and organizations to monitor and conduct research on insects and their relationship to diseases. Diseases experienced by American soldiers during the Spanish American War and the probability of the United States entering World War I, prompted the establishment of civilian and military preventive medicine organizations. The Public Health Service was established in 1912 to combat outbreaks of diseases; it also directed some of its resources toward the control and eradication of epidemics spread by insect vectors.[13] The National Research Council, created in 1916, was tasked by President Woodrow Wilson to mobilize the scientific resources of the country as a preparedness measure prior to entering World War I.[14] A second important agency was founded in 1916, the Committee on Medicine. It was directed by the Council for National Defense to assume responsibility for medical preparedness, which included mobilization, combating venereal disease and research in cooperation with the National Research Council.[15] The Sanitary Corps was established within the Medical Department in 1917. The corps consisted of commissioned officers possessing special knowledge and skills in sanitation, sanitary engineering, bacteriology and other sciences relating to sanitation and preventive medicine.[16] These organizations and other disease oriented agencies developed medical plans and programs to prepare for the military entrance into the World War.

Medical preparations for entrance into the World War were comprehensive. The federal organizations established between 1912 and 1916

directed their collective resource efforts to develop medical plans and programs for reducing the incidence of disease in deployed American soldiers. The medical department, through the medical preparedness program, coordinated the voluntary support of civilian medical professionals, throughout the country, to support the war medically. The combined planning efforts of the medical department and federal agencies resulted in a modicum of success in reducing the incidence of malaria during World War I. Including the malaria statistics of the American Expeditionary Forces sent to Europe under the command of General John J. Pershing, the U.S. Army suffered 15,555 cases of malaria and loss of 200,000 man-days.[17] The malaria incidence rate was 3.77 per 1,000 assigned soldiers.

The possibility of the United States entering World War II caused the federal government to initiate medical preparedness. Massive malaria research and development efforts were conducted from 1942 to 1945. These efforts were spearheaded by the Committee on Medical Research, that was established by the Committee on Medicine in 1941. The committee was responsible for developing an improved antimalarial drug as well as an improved insecticide. Prior to 1942, primary malaria preventive measures included the administration of the antimalarial drug, quinine; and dispersal of the mosquito larvacide, Paris green. The Committee on Medical Research recognized the shortcomings of the current preventive measures, and pursued research to improve them. As a result of large scale coordination, cooperation and collaboration, with several research institutions and industries, two important discoveries were made.

Quinicrine was discovered as a more effective antimalaria drug than quinine; and dichlorodiphenyltrichloroethane (DDT) was discovered as a more effective insecticide than Paris green. The discoveries gave renewed impetus to the faltering malaria prevention program; however, they came too late to have a major impact on soldiers serving in malaria infested theaters of operations. From 1942 to 1945 soldiers suffered 403,689 cases of malaria, with 8,521,535 man-days lost and 330 deaths.[18]

The number of cases of malaria and lost man-days during subsequent wars are:

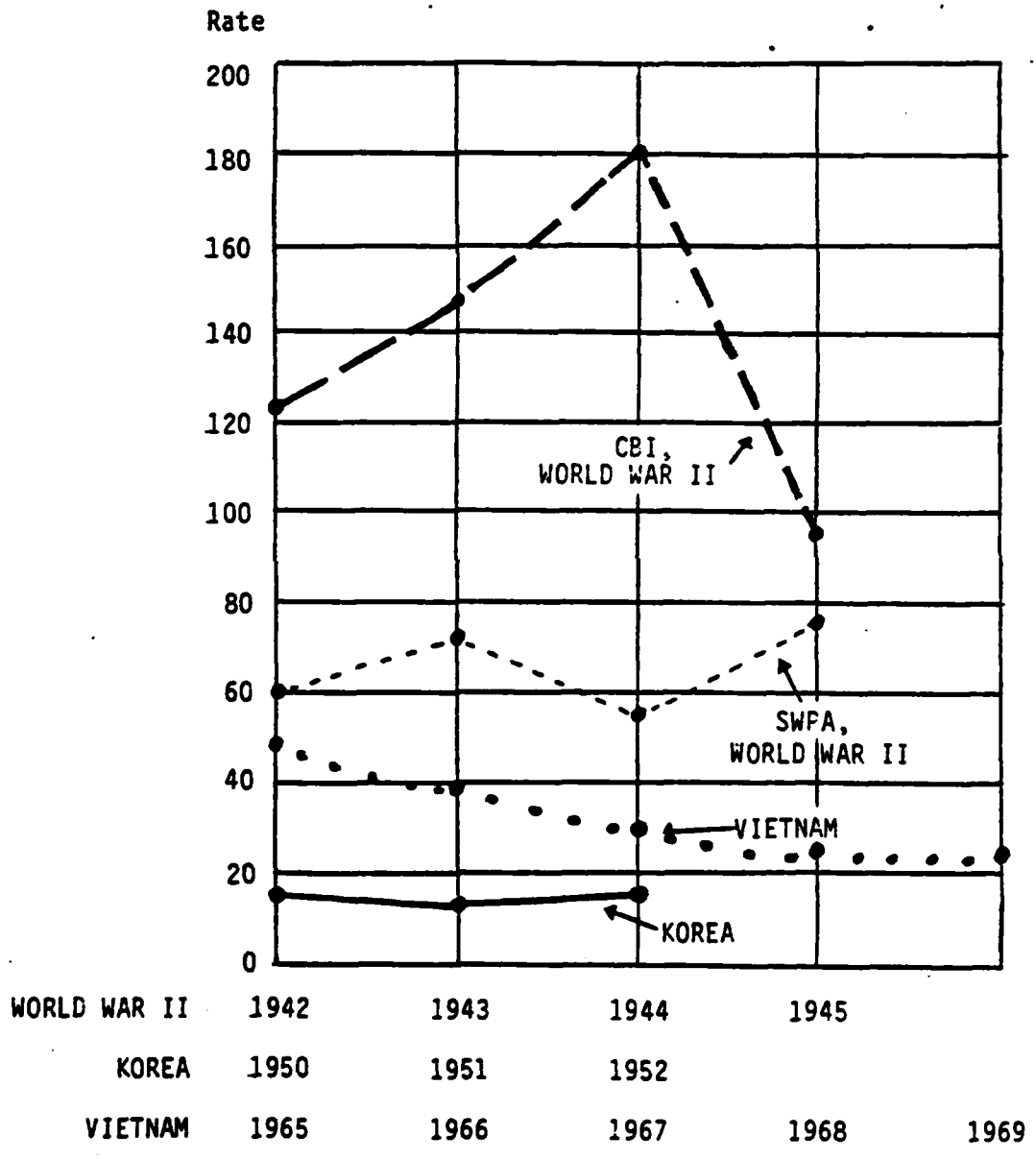
(1) Korean War: 8,686 cases; 260,580 man-days lost; 1 death.[19]

(2) Vietnam War: 40,414 cases; 1,212,420 man-days lost; 78 deaths.[20]

The number of cases of malaria and subsequent loss man-days continued to climb despite development of new antimalarial drugs and insecticides. Figure 1 lists the malaria incidence rate, by year, during the last three wars involving American forces.[21]

FIGURE 1. ADMISSIONS BY YEAR, TO HOSPITAL AND QUARTERS FOR MALARIA IN THREE WARS: WORLD WAR II, KOREA, AND VIETNAM

Rate expressed as number of admissions per annum per 1,000 average strength



The antimalarial preventive measures in effect are inadequate to eliminate the disease. The preventive measures include administering antimalarial drugs, eliminating the anopheles mosquito vector, and enforcing individual protective measures. No single preventive means by itself has been effective. All three measures must be used together to obtain maximum antimalarial protection.

The malaria prophylactic effects of Peruvian bark was recognized during the American Revolution in 1776. The Continental Congress ordered the medical committee to send 300 pounds of Peruvian bark to the Southern Department for the soldiers.[22] Quinine, the active principle of Peruvian bark, was extracted in 1820, which made treatment of malaria easier.[23] The medicinal effects of quinine were limited, however, in that it did not cure malaria, but relieved the fever and other symptoms as well as arrested the disease. Pharmacological research to improve quinine was marginally successful prior to 1941. Two early problems that hindered research progress were locating suitable laboratory animals that were physiologically similar to man; and reducing the excessive side effects which precluded early release of new antimalarial drugs.

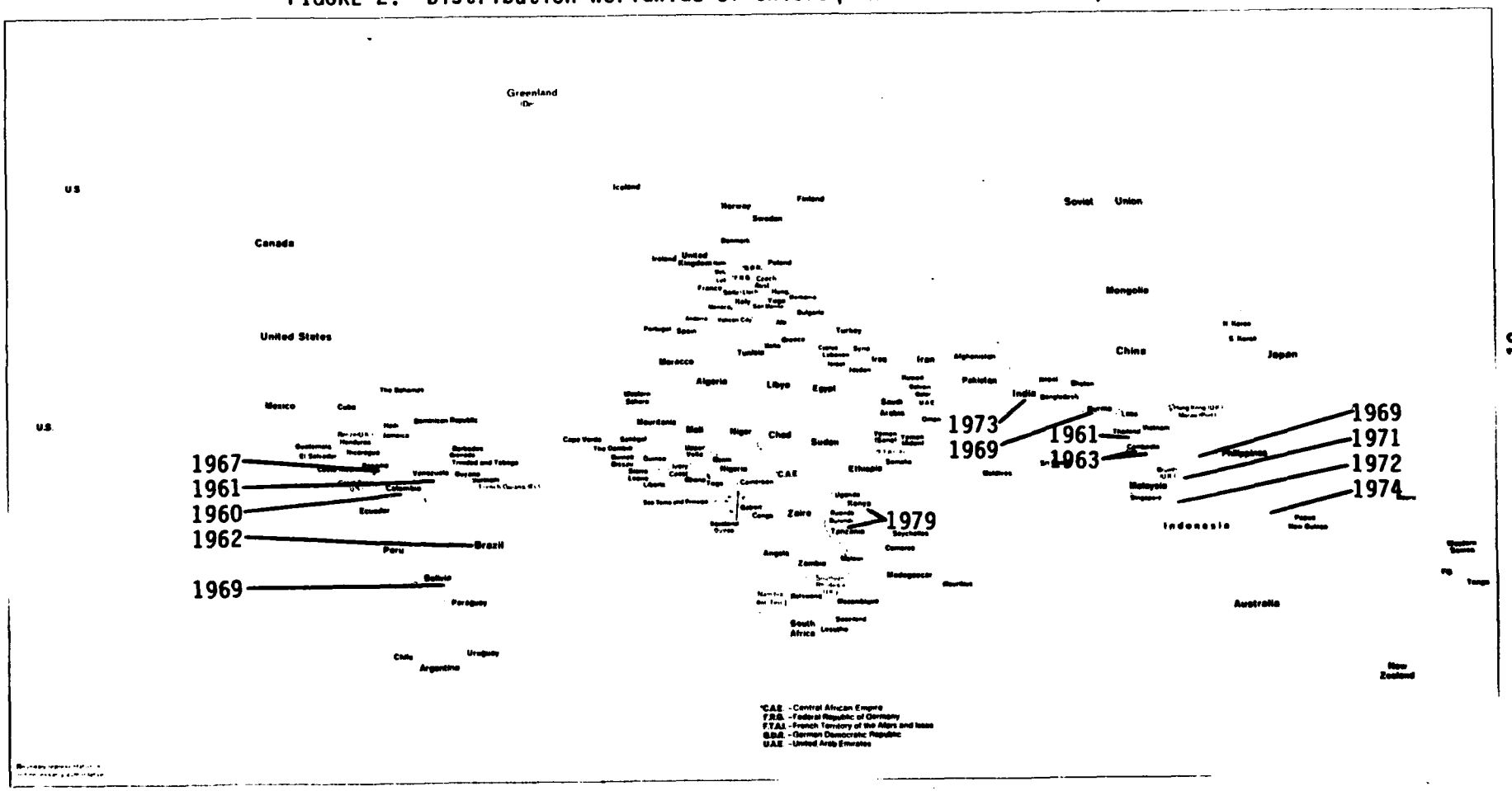
Several methods are used to eliminate the mosquito population. They include dispersing Paris green, petroleum products, and insecticides to destroy mosquito larva; DDT is sprayed to destroy adult mosquitoes. Other preventive methods include draining and covering mosquito breeding areas and covering open containers to avoid water accumulation.

Individual protective measures are important in the prevention of malaria. The correct use of insect repellents and protective screening

equipment are essential during the hours of darkness. Soldiers require continuous education on the proper wear of the uniform. In malaria endemic areas, shirt sleeves and pant legs are worn down to avoid mosquito bites.

The military interest in malaria endemic countries stems from a worldwide deployment mission to protect the vital interests of the United States. Soldiers deploying to malarial endemic regions face a documented risk of contracting the disease if antimalarial preventive measures are not enacted. However, antimalarial preventive measures are being challenged. Many Plasmodium falciparum organisms are resistant to chloroquine, the primary drug of choice. Chloroquine resistance was first discovered in Columbia, South America, in 1960.[24] Since that time, chloroquine resistant strains have been discovered in Southwest Asia, Africa, and other South American countries. (Figure 2 identifies the distribution worldwide of chloroquine resistant Falciparum malaria).

FIGURE 2. Distribution Worldwide of Chloroquine-Resistant Falciparum Malaria



Several species of anopheles are resistant to DDT, the insecticide of choice. As a result of these factors, malaria is resurging in many countries where it was once thought to be eradicated. To overcome the debilitating effects of malaria, soldiers need permanent protection prior to arriving in the endemic areas.

Active immunizations would confer permanent protection from malaria, but no vaccine to prevent human malaria is currently available. This is attributed to limited research on the biology of both the malaria parasite and mosquitoes after World War II. A false sense of security resulted from the belief that environmental preventive measures would eliminate malaria, and the success of the worldwide malaria eradication program of the World Health Organization in 1957 was grossly over-estimated. The worldwide resurgence of malaria in the past decade has rekindled interest in the disease. Research to learn more about parasitology, physiology and serology of the plasmodium is being conducted by military and civilian organizations.

The United States Army Medical Research and Development Command (USAMRDC) was established in 1958 to conduct research on diseases of military interest. The Walter Reed Army Institute of Research (subordinate unit of USAMRDC) started an antimalarial research program in 1964. Since that time, research and development continues in the hope of developing an active vaccine for malaria.

Assumptions And Restrictions

1. The United States will continue to maintain units with world-wide deployment missions in support of national policies. These units

will be vulnerable to contracting malaria.

2. This thesis deals primarily with malaria research and development initiatives of the US Army. Limited research and development efforts of other services and countries are discussed.

3. Emphasis is placed on the impact of malaria disability on combat effectiveness.

4. Conclusions drawn in this paper are the author's and do not represent official Army doctrine.

ENDNOTES

[1]Emory C. Cushing, History of Entomology in World War II (Baltimore: Lord Baltimore Press Inc., 1957) pp. 2-5.

[2]Encyclopedia Americana, 51st ed., s.v. "Malaria", by Paul F. Russell.

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[11]Ibid.

[12]Cushing, History of Entomology in World War II, p. 10.

[13]Ibid., p. 11.

[14]Bayne-Jones, The Evolution of Preventive Medicine in the U.S. Army, 1606-1939, p. 151.

[15]Ibid., p. 148.

[16]Ibid., p. 151.

[17]Joseph F. Siler, The Medical Department of the Army in the World War (Washington, D.C.: Government Printing Office, 1928) p. 511.

[18]Reister, Medical Statistics in World War II, pp. 406-407.

[19]Army Medical Service Graduate School, Medical Science Publication Number 4 (Washington, D.C.: Government Printing Office, 1954) p. 101.

[20]Neel, Medical Support of the U.S. Army in Vietnam, 1965-1970, p. 39.

[21]Ibid., p. 35.

[22]Hume, Victories in Military Medicine, p. 160.

[23]Ibid.

[24]"Experimental Malaria", Military Medicine 134 (September 1969),: 730.

CHAPTER TWO

MALARIA PREVENTIVE MEASURES

Malaria is a parasitic disease transmitted to man by the bite of an infected female anopheline mosquito. Plasmodium sporozoites, from the mosquito, are injected in man along with its salivary juices during the blood meal. The sporozoites are transported through the bloodstream and rapidly invade hepatic cells of the liver.[1] The victim is asymptomatic and does not develop malaria related symptoms, such as fever or chills, for ten to fourteen days. Within the liver, the sporozoite undergo asexual reproduction and develop into merozoites or sexual forms. They rupture out of liver cells and invade erythrocytes or red blood cells.[2] In the erythrocytes the parasites divide into merozoites, each of which is capable of infecting more erythrocytes. This repeated cycle of rupture of liver cells and invasion of erythrocytes by asexual parasites gives rise to symptoms of malaria.[3]

Even though a high percentage of the newly liberated merozoites get through to continue the cycle, a few develop into male and female sexual forms called gametocytes. These forms remain inactive until swallowed by a mosquito which feeds on an infected human for a blood meal. Fertilization occurs in the mosquito's body, and eventually the embryonic parasites travel to the insect's salivary glands, ready to infect a new human victim.[4]

The clinical aspects of malaria have been known for centuries. The symptoms include fever of 103° to 104°F or higher, chills, severe headaches, sweats, myalgias, and prostration. Normally the victim will experience repeated episodes of the symptoms. The duration of the illness may last from 21 - 30 days.

Once malaria is considered a possibility, the diagnosis is confirmed by laboratory results. Thick and thin blood smears are taken several times the first day malaria is suspected, and then on subsequent days for an accurate determination of the infecting species. Infection of more than one malaria parasite is common.

Research and development endeavor to prevent malaria are discussed from a drug, environmental and individual standpoint. The first of these antimalarial preventive measures revolve about drug administration. However, recent medical advances in drug therapy have expanded their concept and now address immunization to include active and passive immunity. Thus, three aspects of drug therapy include antimalarial chemotherapy, active immunization, and passive immunization. Environmental malaria protective measures focus on dispersing insecticides and draining and covering mosquito breeding areas. Individual protective measures are those precautions the individual soldier can take while at work and at rest. Soldier discipline problems are encountered with both antimalarial drug administration as well as following prescribed individual protective measures. Documented discipline problems stem from the soldier's failure to take the antimalarial tablet and lack of compliance with individual protective measures.

Drug Related Preventive Measures

A general description of immunology aids in understanding the mechanics of protection conferred by active and passive immunizations and antimalarial drugs. Immunology is a field of science concerned with the development of immunity and related biological processes. The ability of a human or an animal to react defensively against a foreign substance, by destroying or neutralizing it, is called immunity. Antigens or foreign substances that enter the body stimulates the production of an antibody, which is a protein, that unites with the antigen and renders it subject to destruction by other members of the reticuloendothelial system.[5]

Antimalarial Drug Suppression

Antimalarial drugs are chemotherapeutic agents administered orally to prevent or cure malaria. The efficacy of any antimalarial chemotherapeutic agent results from its ability to interfere with or participate in some phase of biological activity of the parasite. In addition, the drug must be able to reach the specific site of the infection, achieve a static or building concentration at the site, and maintain a biologically active concentration for lengthy periods of time.[6] Early speculation concerning the mechanism of the antimalarial actions of the cinchons alkaloids (quinine, quinicrine, etc.) was that it had no direct action on the plasmodia, but interfered with the biologic system within the parasitized erythrocyte that is essential for the growth and multiplication of the parasite.[7]

Research with quinicrine demonstrated that benign tertian malaria (Plasmodium vivax) and the malignant tertian variety (P. falciparum)

could be effectively suppressed by quinicrine if certain minimal plasma drug concentrations were continuously present. Drug administration schedules are drawn up for soldiers which guarantee the maintenance of protective concentrations without loss of effectiveness due to toxic symptoms.[8]

Chloroquine is the military drug of choice for preventing and suppressing vivax and sensitive strains of falciparum malaria. Chloroquine should be administered to each soldier prior to being deployed to a malarious endemic area. Within hours the plasma drug concentration is sufficient to resist the malarial parasite. A dose of chloroquine is taken at least one day prior to exposure to be effective and it is taken weekly while in the malaria endemic area. After returning from the endemic area, antimalaria chemoprophylaxis should continue for four weeks. If chloroquine alone is used, a two week course of primaquine is required as a terminal prophylaxis. Pyrimethamine - sulfadoxine (Fansida) or mefloquine are the drugs of choice in areas with chloroquine resistant strains of Plasmodium falciparum. In Vietnam, a chloroquine-primaquine combination was used to prevent malaria, except in soldiers that experienced adverse reactions due to glucose-6-phosphate dehydrogenase deficiency (G6PD). Patients with G6PD deficiency may experience a hemolytic anemia from primaquine, necessitating a reduction of drug dosage.[9]

Medical discipline problems are encountered when antimalarial drugs are administered. Soldiers fail to take their weekly chloroquine-primaquine (C-P) tablet as prescribed. Several reasons have been given for this failure in taking the medication. During the early phases of

the Korean war, the fast-moving tactical situation and supply problems made it difficult to institute a complete program.[10] The situation was improved later during the Korean conflict. In Vietnam different reasons were given for failure to follow the drug regimen including unavailability of tablets, fear of gastrointestinal side effects, and willingness to contract a non-fatal disease to avoid field duty.[11] Several programs were instituted to overcome discipline problems. These programs included reeducation, urinalysis testing, designating a C-P tablet day, and supervising administration of the tablet by non-commissioned officers. Discipline problems continued to contribute to increase in the incidence of malaria, and subsequent reductions in unit effectiveness.

Active Immunization

Active immunization consist of injecting the actual foreign substance into the host, and his body forms antibodies against it.[12] It is hypothesized that an active immunization will confer protection on soldiers for long periods of time, i.e., years. Active immunization with human volunteers has been conducted on a limited scale. In one documented experiment (Clyde, et al.), mosquitoes harboring sporozites of Falciparum malaria were X-irradiated with 15,000 rads.[13] Irradiated mosquitoes fed on three human volunteers, with no previous exposure to malaria, for 84 days. Fourteen days were alloted for protective titers or concentrations to accumulate. On day 98 serum samples were taken from the volunteers and examined using the indirect flourescent antibody (IFA) method. The dilution endpoints were 1:5 for P. falciparum and 1:10 for

P. Vivax. Also, on day 98 nonirradiated mosquitoes with a homologous strain of P. falciparum fed on volunteers. One volunteer did not develop malaria and continued to be immunized for seven months. During this period, however, he was exposed to more irradiated mosquitoes carrying sporozoites through day 315. On day 327, he was challenged again with nonirradiated mosquitoes, but he did not contract malaria. A serum sample was collected on day 327 and examined for malaria antibodies: the IFA serum dilution endpoints were 1:10 for P. falciparum and 1:10 for P. vivax. After remaining malaria-free for two months, with IFA serum dilution endpoints of less than 1:5 for P. falciparum and P. vivax, he was injected with blood trophozoites for P. falciparum. The volunteer developed malaria in seven days.[14]

Antisporozoite antibodies were first detected by the circumsporozoite precipitation test on day 327. The test clearly demonstrated the successful active immunization of man to falciparum sporozoites of the same strain.[15]

Passive immunization is the transfer of protection by the injection of antitoxins or other antibodies in the blood serum.[16] No passive immunizations of humans for malaria have been successful. Normally, passive immunizations confer protection for several weeks.[17] Even if a vaccine for passive immunization were available, it would be prohibitive to administer repeatedly to large numbers of soldiers in a combat environment.

ENVIRONMENTAL CONTROL MEASURES

Throughout American military history, environmental control

measures have been used to reduce the incidence of malaria, and is accomplished by eliminating the infective Anopheles mosquito population. Dispersal of insecticides to destroy adult mosquitoes and their larvaes as well as drainage and coverage of mosquito breeding areas are commonly used environmental control measures.

Dispersal of Insecticides

Insecticides have played a major role in eliminating the anopheles mosquito population in many parts of the world. L. Howard discovered in the 1880's that kerosene spray killed mosquito larva. Since that time, other petroleum sprays, Paris green (compound of copper, arsenic and acetic acid), and phenothiozene have been used as larvacides. These larvacides were effective, but had no effect on adult mosquitoes. In addition, they are not practical for dispersal over large swampy areas with available equipment. Paris green produced limited results in reducing the incidence of malaria in World War I. After World War I, the airplane was tested for dispersion of Paris green. The success of the test led to dispersal over large areas of difficult terrain and expedited the larva destruction process.[18]

Even with the successes of airplane dispersal of insecticides, the need for a more efficient and practical insecticide was realized. The discovery of dichlorodiphenyltrichloroethane (DDT) in Orlando, Florida, in 1942 gave renewed impetus to the mosquito eradication problem. The insecticide killed the larva and adult mosquitoes, was 25-100 times more effective than Paris green as a larvacide, and had a long-lasting killing effect.[19]

The practicality of DDT was helpful during World War II. Two quarts of a 5-percent solution of DDT in kerosene or fuel oil did the same job when sprayed as it took one to two pounds of Paris green or 25 to 50 gallons of oil to accomplish.[20] The shipping space required was greatly reduced, which was always a premium. Aircraft and ground vehicles were rigged with DDT dispersal equipment which enhanced dispersal over large areas and limited terrain. As a result, DDT was used during the Korean and Vietnam wars with success in inaccessible areas.

Since its discovery, DDT has been extremely effective in reducing the mosquito population. The result is overall reduction in the incidence of malaria. However, anopheline mosquitoes resistant to DDT have been encountered in many parts of the world. In Indonesia and the Soloman Islands fenitrothion is used to control A. acouitus and A. faranti respectively.[21]

In some countries insecticides such as malathion and propoxur are used to kill DDT-resistant mosquitoes, but the insects are already showing signs of developing resistance to the newer chemicals.[22] Mosquito resistance appears to be a consequence of the widespread use of insecticides.[23] This problem poses a major threat to malaria eradication programs and is contributing to the resurgence of malaria.

Drainage and Coverage of Mosquito Breeding Areas

Mosquitoes breed and grow in water that is stagnant, slowly flowing, brackish, fresh or even salt in some areas.[24] The favorite breeding place of the anopheline is water containing green algae

growth.[25] Draining and covering small breeding areas with earth and draining and dispersing mosquito larvacides on large areas are effective in reducing and eliminating the mosquito population. The positive effects of drainage were realized as early as the 1880's, when T.J. Headlee published a bulletin on the mosquitoes of New Jersey and pioneered the control of the salt-marsh species by the draining of tidal marshes.[26]

Though peacetime surveillance and control of malaria breeding areas are effective, this presupposes that medical intelligence on the area is acquired in a timely manner. Swampy areas can be drained and covered or sprayed with insecticides as appropriate, but this task is not easy to accomplish because of the time and effort required to complete the work. In addition, it is not feasible to identify all breeding areas nor reach them, and in an active combat environment, the feasibility of employing drainage and earth coverage on a large scale is impossible. Potential hazardous areas can be identified early and a course of action determined to combat the mosquitoes, but executing it is difficult because of the demands of combat. These preventive measures can only be employed in the base camp areas, but will provide little assistance to combat arms soldiers.

Individual Protective Measures

Individual protective measures are those which must be used by the soldiers to avoid malaria. Soldiers must constantly be reminded of the debilitating effects of malaria and how they can prevent it. Individual

protective measures can be applied when the soldier is at work and at rest.

Correct wearing of the combat uniform provides a large measure of protection to soldiers while at work. The pants are loosely fitted and tucked into the boots without blousing garters and the shirt is buttoned with the sleeves down. Mosquitoes can bite through clothing worn tightly against the skin. When available, uniforms impregnated with M 1960 should be worn to repel mosquitoes.[27] Soldiers are not allowed to wear shorts as an outer garment from dusk to dawn, and not allowed outdoors without a shirt during this period. Insect repellents such as DEET is placed on exposed body parts to repel mosquitoes, and headnets afford excellent protection from mosquitoes during the hours of darkness.

Screening devices have provided protection against adult mosquitoes while the soldier is at rest. The currently used screening equipment is made of either wire or soft fabric and should be kept in good condition at all times.[28] The bednet is the most widely used mosquito screening device and a necessity in malarious areas. Mosquitoes can bite through nets when the soldier's body is in direct contact with it. To curtail this risk, the bednet should be sprayed prior to use. The importance of the mosquito net can not be overemphasized. Field Manual 21-10, Field Hygiene and Sanitation, stresses the importance of the mosquito net and recommends that the net be carried as personal equipment by all soldiers entering a malarious area, even in forward combat areas.[29]

The efficiency of individual protective measures is directly proportional to the discipline level of the soldiers. Commanders must be

aware of and strictly enforce individual protective measures, particularly placing bed nets over their sleeping areas. The restrictive nature of the protective devices often cause the soldier to look upon this equipment as a hindrance rather than a help.[30] Thus, rigorous command emphasis should be placed on appropriate use of these valuable protective measures.

Comparative Analysis of Malaria Preventive Measures

Malaria preventive measures are used in concert with each other to obtain maximum effectiveness. Individual protective measures and environmental controls greatly enhance the effectiveness of antimalarial drugs. The soldier discipline problems associated with both the individual protective measures and the antimalarial drugs have placed avoidable demands on personnel resources. Supervisory personnel will be required to operate the urinalysis program, administer the chloroquine-primaquine tablet on a prescribed day, and monitor compliance with individual protective measures. However, even with supervisory personnel monitoring discipline problems during the Vietnam War, antimalarial protective measures used were partially successful.

In the active combat zone, environmental measures to control the mosquito population will be limited. The tactical situation, by its very nature, will prohibit sanitation personnel from spraying insecticides and draining many mosquito breeding areas. This problem might be compounded by the requirement for repeated applications of the insecticides. In addition to insecticide application, the logistics system may not be able to replenish the supply of insecticides in the forward combat areas.

Ideally, active and passive immunizations are the preferred methods of preventing malaria. Of the two methods, active immunization is more feasible. Active immunization of sporozoites in humans has been observed, but further research is required. On the other hand, only limited research has been conducted on passive immunizations, and none on humans. Active immunizations will confer long lasting protection from malaria and not require repeated administrations. Thus, the soldier can be immunized prior to deployment and prepared for continuous operations in the malaria endemic area without fear of contracting the disease. In addition, no requirements are placed on the logistics system for resupply and soldier discipline problems are eliminated. Active immunizations will not depend on other environmental control measures to be effective.

The matrix at Figure 3 depicts a comparison between different malarial preventive measures. It clearly supports active immunization as the preferred method to prevent malaria. An explanation of the states of nature in the matrix are:

(1) Predeployment protection: the soldier receives protection against the malarial parasite, prior to departing the continental United States or an intermediate staging base, enroute to a malaria endemic area.

(2) Protects in the malarial endemic area: the soldier will not contract malaria even though it is a problem with the civilian populace.

(3) Depends upon other preventive measures for maximum effectiveness: the efficacy of the preventive measures is greatly reduced when used alone.

(4) Ease of administration: requires less planning, coordinating, and monitoring to execute.

(5) Require repeated administrations: the preventive measure must be repeated at specific intervals in the endemic area to remain effective.

(6) Poses discipline problems: monitoring of the soldier is required to ensure he is conforming to the preventive measure.

(7) Poses logistical problem: special equipment, cargo space, and special handling procedures are required to transport the contents of the preventive measure to the user.

(8) Readily available: the equipment and supplies to initiate the preventive measure are currently in the U.S. Army's inventory.

(9) Theoretical probability of development: research initiatives are ongoing to develop or improve the preventive measure.

FIGURE 3 - Comparative Analysis of Malaria Preventive Measures

	Active Immuni-zation	Passive Immuni-zation	Anti-malarial Drugs	*Indiv. Prot. Meas.	**Envir. Prot. Meas.	Weight
Predeployment Protection	1(1)	1(1)	2(2)	3(3)	3(3)	1
Protect in Malaria Endemic Area	1(2)	1(2)	1(2	2(4)	2(4)	2
Ease of Administration	1(2)	1(2)	1(2)	2(4)	3(6)	2
Requires Repeated Administrations	1(1)	2(2)	3(3)	3(3)	3(3)	1
Poses Discipline Problem	1(1)	1(1)	3(3)	3(3)	3(3)	1
Depends on Other Preventive Measures for Maximum Effectiveness	1(1)	2(2)	2(2)	3(3)	3(3)	1
Readily Available	3(6)	3(6)	1(2)	1(2)	1(2)	2
Theoretical Probability of Development	1(2)	3(6)	1(2)	1(2)	1(2)	2
Sum	18	24	24	30	30	

* Individual Protective Measure
** Environmental Protective Measure

ENDNOTES

Chapter II

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CHAPTER THREE

IMPACT OF MALARIA ON RAPID DEPLOYING FORCES

During a crisis, a decision by the National Command Authority (the President and Secretary of Defense or their designated representatives) may result in overseas deployment of military forces to protect interests of the United States. The Joint Operations Planning Systems Manual, Volume IV, defines a crisis as:

> ...an incident or situation that rapidly develops external to the Continental United States, and creates a condition of such diplomatic, political, or military importance to the U.S. Government that commitment of U.S. military forces is contemplated to satisfy objectives.[1]

In order to provide a military response to a crisis, the Rapid Deployment Joint Task Force (RDJTF) was activated on 1 March 1980. Even though the RDJTF was initially established during the Carter Administration to respond to a crisis in the Persian Gulf Region, its mission has since been expanded to respond to global crises. As a result, the RDJTF is subject to deployment worldwide to protect interests of the United States, including those areas identified as responsibilities of pre-designated commander-in-chiefs.

The United States has varied interests in numerous areas of the world. An interest for the purpose of this thesis is an expression of what a nation needs or wants in relation to matters of international concern.[2] It may be what is needed or desired in reference to a specific

situation, region or issue, or it may be vital.[3] A vital interest arises out of the very existence of a state including its survival and independence, deterrence of and defense against attacks and the protection of its economic and political systems.[4] In short, a vital interest is worth fighting for.[5]

The United States has interests in the regions of sub-Saharan Africa and Latin America. They are political, economic, strategic, and military interests. Malaria endemics are prevalent in many countries of sub-Saharan Africa and Latin America, to include chloroquine-resistant strains of Plasmodium falciparum. The ability of the RDJTF or any ground contingency force to conduct continuous operations in either country is dependent on viable malarial protective measures. Historically, malaria has caused a high noneffectiveness toll on American forces in both regions. Unless a vaccine for malaria is developed, there is no logical reason to believe that the malaria trend will change during future deployments of U.S. forces to sub-Saharan Africa or Latin America.

SUB-SAHARAN AFRICA ASSESSMENT

United States Interests in Africa

The U.S. interests in Africa are many and varied, spanning the spectrum of political, strategic, and economic concerns. They include every geographical area of the African Continent from the Cape of Good Hope to the Mideast front-line states and from the Horn to Cape Verde.[6]

With the continual emergence of independent countries since the 1960's, Africa has transformed the character and scope of international affairs. African nations play a significant role in seeking change in

the international order through active participation in the United Nations and conferences with nonaligned countries.[7] In multiple aspects of political interests, the United States has an interest in African support of the law of the sea and nuclear nonproliferation. Both Congress and the business community believe that mineral supply interruption could occur because of political instabilities in the region or the accession to power of unfriendly governments that cooperate with the Soviet Union to manipulate world mineral supplies for political or economic advantage.[8]

United States strategic interests in sub-Saharan Africa are significant, and in many ways influence U.S. African policy. The world's key shipping routes to Middle Eastern oil for Europe and America require negotiating oceans around the African Continent.[9] As a result, Africa littoral states are of geopolitical interest to western oil importing powers and the Soviet Union.[10] United States Naval and Air Force access to ports and bases respectively, in black Africa, are important dimensions in defining the United States strategy in the Indian Ocean and southern Atlantic area.[11] The United States maintains tracking station rights and house Voice of America transmitters as well as relay stations in several African countries. The paramount strategic importance of sub-Saharan Africa is key to execution of U.S. strategies in other areas of the world.

Economic interests in sub-Saharan Africa includes purchasing minerals, procuring oil, increasing trade and promoting internal development. Several countries of sub-Saharan Africa are the main source of many minerals which are vital to development and defense of the United

States. They supply the majority of our demands for chrome for automobiles and defense industries, manganese for the steel industry, cobalt for jet engines and mining equipment, and several precious minerals, including industrial diamonds.[12] Nigeria is the second largest supplier of oil to the United States; Saudia Arabia is the largest supplier. Of $14 billion imports from African countries in 1979, purchasing of petroleum from Nigeria amounted to $8.6 billion dollars.[13] The United States also purchases oil from Gabon and Angola. Countries of sub-Saharan Africa bought more than $3.2 billion worth of commodities, technology, and equipment from the United States.[14] Though trade with sub-Saharan Africa is not overwhelming considering total U.S. imports, combined with other interests and the Soviet objectives in the region, trade is significant.

Soviet objectives in sub-Saharan Africa are: disrupting Western influence in Africa; controlling sea lanes around Africa and access to the Persian Gulf in the event of conflict; promoting dependency on the Soviets among African states and revolutionary groups; and establishing a strong conventional presence in the Indian Ocean.[15]

Malarial Threat and Implications

The basic operational concept of the Army is called AirLand Battle doctrine, which is based on securing or retaining the initiative and exercising it aggressively to defeat the enemy.[16] The ability of the Rapid Deployment Joint Task Force (RDJTF) or any ground contingency force to deploy and conduct continuous operations to protect U.S. interests in sub-Saharan Africa, will be ameliorated because of the malaria threat.

Malaria is endemic in sub-Saharan Africa and remains one of the most wide-spread communicable diseases. About 90 percent of Africa is tropical, which is the highest percentage for any country, since it lies astride the equator with Tunnis 2,400 miles to the north and Cape Town 2,600 miles to the south.[17] The tropical climate of Africa is the major contributing factor to the malarial incidence rate of 110 million cases annually among the civilian populace.

Falciparum malaria, which is the most fatal to casualties, is not new to American forces deployed in Africa. During World War II the malaria incidence rate was 77/1000 assigned personnel in the African-Middle East Theater.[18] However, chloroquine resistant Falciparum malaria, which was discovered in East Africa in 1979, represents a severe health risk for American forces deployed in the region.[19] Renewed emphasis must be directed towards countering the malaria threat.

Several factors contribute to the current high incidence of malaria in sub-Saharan Africa. The worldwide malaria eradication program of the World Health Organization was and continues to be unsuccessful. None of the economically feasible methods of vector control or drug administration, or both, permitted a major reduction in malaria transmission, let alone interruption.[20] The interaction of climatic and hydrological factors during certain periods of the year cause large segments of the population to be isolated due to inaccessability. Besides the plateau landforms in Africa, other impediments to overland movement are: the heavy seasonal rainfall over most of the area, which makes a large number of roads dangerous or impassable during parts of the year; dense forest growth in the rainforest regions; and the absence of

ballast, where it is needed.[21] The high vectorial efficiency of the Anopheles gambia and its apparent resistance to insecticides is a fifth contributory factor. Many anopheles mosquitoes previously thought to belong to a single species, are in fact complexes of various sibling species, each with its own behavorial characteristics and plays a different role in the transmission of malaria.[22] The final contributory factor is socioeconomic which includes inadequate development of health services and health manpower, financial constraint, and lack of government commitment to the eradication program.[23]

The malarial problem in sub-Saharan Africa is the largest malarial problem in the free world. This is true despite past and present initiatives by the WHO to eradicate it through institution of their special programs. The WHO admits that it is technically impossible to eradicate malaria in most parts of the African continent, but feasible on certain islands. On Cape Verde and Mauritus a reintroduction of the disease has occurred after the initial success in its eradication.[24] Deployment of American forces to sub-Saharan Africa to protect the interests of the United States, utilizing current malarial preventive measures, render them vulnerable to contracting the disease.

LATIN AMERICA ASSESSMENT

United States Interests in Latin America

The United States has strategic, political, military, and economic interests in Latin America. Primary strategic interests in Latin America are: a level of strategic equilibrium to preclude contingencies requiring major diversion of resources; access to bases, facilities and

line of communication; and access to resources and markets.[25] In addition, the Soviets recognize Latin America, particularly the Caribbean Basin, as the strategic underbelly to the United States and the Achilles Heel of the North Atlantic Treaty Organization, both in peacetime and in war.[26]

The political interests of the United States stresses cooperative relations with the multiplicity of nations, supports aspirations for human rights and democracy, and for the fashioning of an Inter-American Community to achieve common international objectives. However, the emergence of more self-confident and assertive nation-states in Latin America have resulted in a decline of United States political dominance in the region.[27] Yet the United States depends on Latin America in securing support of regional states for her foreign and domestic policies.

Military interests in Latin America include access to air and naval facilities, conduct of military training, and conduct of surveillance activities. The importance of being able to air-stage rapid deploying forces in the Caribbean Basin, area south of the basin, and to Africa gives added importance to airfields in Puerto Rico and Guyana, bases in the Canal Zone, and facilities in Brazil.[28] Military training is conducted at several Caribbean bases in the Canal Zone and Puerto Rico, such as the Armys' Fort Gulick School for the Americas, and the Jungle Warfare Training Center. The United States Navy maintains and operates undersea surveillance systems and undersea test and evaluation centers, invaluable to antisubmarine developments, in the Bahamas.[29]

Finally, a major continuing United States interest in Latin America is economic; oil, raw materials, markets, and investments. Oil

and other petroleum products are obtained from Mexico and Venezuela. The U.S. imports metallurgical bauxite from Jamica and Surinam, refractory bauxite from Guyana and Surinam, copper from Chile, and tin from Bolivia. Also, limited quantities of precious metals, many of importance to the defense electronic industry, are imported from the region, including mercury, silver, platinum, palladium, and industrial diamonds.[30]

Malarial Threat and Implications

Rapid deploying forces, for protection of United States interests in Latin America (includes South America, Caribbean states, Central America and Mexico), will experience numerous casualties because of malaria. Malaria is no stranger to American forces deployed to Latin America; they suffered casualties at a rate of 42/1000 assigned personnel in the Latin American Theater during World War II.[31] The malaria worldwide eradication program of the 1950's and 1960's, unlike in Africa, was successful. However, the development of insecticide resistance among anopheline mosquitoes, drug resistance among plasmodium species, and poor socioeconomic conditions in endemic areas, have contributed to the resurgence of malaria.

Probably the most dramatic resurgence of malaria has been in Central America. El Salvador, most densely populated and poorest of the Central American countries, experienced an increase from 66,691 cases in 1934 to 83,290 in 1976.[32] Malaria cases in Honduras rose from 7,503 in 1974 to 30,289 in 1975 and 48,804 in 1976.[33] Other Latin American

countries reported a significant increase in cases of malaria during the 1970's.

The malarial parasite of Latin America exhibits widespread resistance to antimalarial drugs. Chloroquine-resistant strains of falciparum malaria is found in both Central and South America. These chloroquine-resistant strains of Plasmodium falciparum are not only resistant to 4-aminoquinoline drugs, but also resistant to pyrimethamine/sulphonamide combinations in South America.[34] This combination of antimalarial drug was the only satisfactory operational formulation for use against chloroquine-resistant malaria.

Resistance of the Anopheles mosquito to insecticides also contribute to the resurgence of malaria in Central America. This increase is not only attributed to intensified use of insecticides on crops, but to created mosquito breeding areas from inadequate water management in irrigation schemes.[35]

Influence of Malaria Disability on Combat Effectiveness

The ability of the Rapid Deployment Force to conduct sustained operations in sub-Saharan Africa and several parts of Latin America will be influenced by the malarial parasite. The documented resistance of Plasmodium falciparum to chloroquine and the 4-aminoquinolines compounds as well as resistance of the Anopheles mosquitoes to insecticides, suggest that malaria will hamper military operations in either area.

The modern battlefield has made quantum leaps in sophistication of weaponry and doctrine over the past decade, and will continue in the future. The battlefield of the future will be dense with combat systems

whose range, lethality, and employment capability will surpass anything known in contemporary warfare.[36] This advancement has set the stage for short, very intense wars characterized by continuous operations, which has been the thrust of Soviet doctrine since the 1950's. From 1971-1981 the cumulative dollar cost of Soviet defense activities has exceeded that of the United States by more than 40 percent, and the Soviets currently outnumbers the United States in many major weapon systems.[37]

President Reagan's 1983 budget request, with an increase in defense appropriations, is an acknowledgement of the longstanding policy of the Soviet Union to modernize her forces. The force modernization program ongoing in the United States is the most comprehensive since World War II.[38] More than 500 new weapons and equipment systems are scheduled to become operational in the future. If unimpeded by Congressional fund cutbacks and changes in plans, virtually no aspect of how the Army goes to war will be the same when the present modernization program is complete.[39]

Dedication to the force modernization effort is reflected in the accelerated schedule of actual and planned new equipment arriving in various units as follows: the M-60A tank and M-198 howitzers entered operational status in units in 1979 and 1980 respectively; in 1981 the Abrams M-1 tank, the AN/TPQ-36 Firefinder and the Stinger were fielded; in 1982 the Copperhead became operational; and in the future the improved TOW and the Bradley fighting vehicle will be entering the fighting inventory.[40] The Army's ability to conduct future operations depends fully on continuation of modernization in doctrine, force structure, and

equipment in order to accomplish many diverse tasks.[41] Yet, force modernization presents several training challenges, which include training individual soldiers to effectively employ and maintain more complex, lethal, and expensive equipment as well as assist units in attaining and maintaining required training standards in difficult situations.[42] Training other than primary operators, to handle modernized weaponry in a malarious area, presents formidable challenges.

Effects of Malaria on Combat Arms Units

Throughout history malaria has had a devastating effect on combat arm soldiers. As the war in the Pacific progressed, during World War II, the incidence of malaria forced the withdrawal of one combat unit after another as forces were "island hopping" to accomplish the mission. Estimated from 1942-1945 time lost in all theaters by Army combat troops because of malaria is approximately 10,140,872 man-days.[43] A total of 11,727 cases were reported by the Navy, the majority of which occurred among Marine combat troops.[44] Malaria was the most significant medical problem encountered in Vietnam. Slightly more than 80 percent of all cases of malaria occurred in combat units and at least two maneuver battalions were rendered ineffective by malaria.[45]

Combat arms soldiers, because of their unit missions, must meet stringent physical and mental qualifications to obtain their military occupational specialities. The duties of armor and infantry soldiers place an extremely high premium on aggressive and offensive spirit geared to the speed and violence of the modern battlefield. In order for combat arm units to accomplish their missions, heavy reliance is placed on the

efficiency of selecting, targeting, and firing crew-served weapons. Weapon crews train together in peacetime to gain and maintain proficiency in a combat environment. Yet, considering the sophistication of today's weaponry, how effective is a crew after one and/or more of its members have been evacuated to the rear for hospitalization due to malaria? The absence or noneffectiveness time of 21 to 30 days initially, coupled with the possible loss of additional days due to relapse of the disease, will impair the effectiveness of the crew.

The mission of the armor division is to destroy Threat armed forces and to control land areas including populations and resources.[46] This mission is accomplished with the employment of tightly integrated crews using fire power, maneuver, and shock effect, in coordination with other combat arms. The tank crew consists of a driver, loader, gunner, and crew chief; all have specific responsibilities which are executed to form the crew into an effective fighting team. The critical element of effective tank gunnery is effective teamwork, which is essential to speed of engagement and accuracy of fire.

The teamwork effort and effectiveness of a crew that has trained together in peacetime is reduced by loss of a crewmember to malaria. Even though crew members are required to be crosstrained, their effectiveness is reduced by the loss of an assigned crewmember, and a replacement will only bring the effectiveness level up as time progresses. But what is even more important, while the unit is engaged in either offensive or defensive operations, is that the crewmember is not aware that he is a victim of malaria. The symptoms will not occur until the plasmodium has undergone its incubation period of 10 to 14

days. The higher the incidence of malaria among tank crews, the lesser the contribution of firepower to the combined arms effort and mission accomplishment.

Tank gunnery standards for crews are established by FM 17-12, Tank Gunnery.[47] Before a crew can be formed into an effective fighting team, the driver, loader, gunner, and tank commander must each be highly proficient in his job. A review of individual crew tasks reveal the following: eleven tasks for the driver; thirteen tasks for the loader, in addition to driver tasks; twelve tasks for the gunner, in addition to driver and loader tasks; and fifteen tasks for the tank commander, including driver, loader and gunner tasks. In any situation, a tank section consisting of two ot three tanks, under the section leader's direction, should be able to: engage multiple targets in priority of danger to the section, with appropriate weaponry; shift section fires within ten seconds to suppress an area target; employ suppressive fires; and maneuver, using terrain to maximum advantage to destroy multiple targets.

The mission of the infantry division is to destroy threat armed forces and to control land area including population and resources.[48] The infantry is most effectively employed in terrain favoring dismounted operations such as large urban areas and jungles. The duties of infantry soldiers involve proficient employment of individual and crew-served weapons and armored vehicles by personnel organized in a series of closely coordinated teams that close with the enemy by means of fire and maneuver to destroy or capture him or repel his assault.[49] Unfortunately, urban areas and jungles are ubiquitous with mosquito

vectors harboring the malarial parasite. The effect of malaria on infantrymen employing either individual or crew-served weapons will reduce markedly the unit's ability to accomplish the mission, particularly the heavy antiarmor weapon infantryman.

A member of heavy antiarmor crew-served squad employs tube-launched, optically tracked, wire-guided (TOW) missiles in both offensive and defensive combat operations. The TOW squad consists of one TOW system and the squad leader, gunner, assistant gunner, and ammunition bearer. The primary mission of the TOW squad is to destroy enemy armor, but it is also effective against point targets such as bunkers and crew-served weapons.[50] Considering the TOW's primary mission, its range can be exploited since it is more accurate than tanks at ranges beyond 1,500 to 2,000 meters, and decreases their vulnerability to detection and return fire. This advantage, or standoff, will not be capitalized on as crew members contract malaria and require evacuation to Corps hospitals. The effectiveness of the crew to target and engage enemy armor will be reduced for specified periods of time, depending on leadership and training level of the squad. Even though mission reduction of the TOW squad, caused by malaria, is used as an example, a similar mission reduction could occur with the mortar squad or infantry fighting vehicle squad.

Effects on Logistics Support

Malaria affects logistic support units by soldiers contracting the disease and by taxing the logistics system in managing malaria casualties. Historically, the incidence rate of malaria on combat service support soldiers has been extremely low compared to the incidence rate in combat units. This was particularly true during the Korean War and the

Vietnam War. Logistical support units such as those assigned to the Division Support Command (DISCOM) and Corps Support Command (COSCOM), by doctrine, are located sufficiently to the rear of the forward edge of the battle area. The relatively fixed locations of medical, maintenance, supply and services, and transportation units allow them to incorporate more effective malaria control measures than combat units. However, requirements to "push" supplies forward and provide maintenance and other services to sustain the combat units, allow a periodic breakdown in malaria control discipline. An insignificant number of combat service support soldiers may contract malaria.

Sustainment of the combat force with adequate supplies of all classes, timely maintenance support, comprehensive medical support, and prompt personnel replacements are paramount to accomplishing the mission. Providing adequate logistical support during major wars always has presented formidable challenges, not even considering the added burden of coping with malaria. However, the primary theme of this section is not to address malaria as it affects combat service support soldiers, but rather consider several of the challenges resulting from managing malarial casualties. Intrinsic demands are placed on medical and personnel units while managing malaria casualties.

Field Manual 101-10-1, Staff Officer's Field Manual Organizational, Technical and Logistical Data, provides general guidelines for estimating theater hospital bed requirements, stockage levels of medical supplies, and calculations on daily personnel losses.[52] Based on the number and type of major maneuver units trooplisted, as well as type of employment operation, the logistics

planner can calculate estimates on functional support requirements and determine the number and type of nondivisional units that are required to sustain the force. After completing the logistics estimate, the shrewd planner consults Field Manual 101-10-2 and other documents to identify the number and type unit needed to logistically support the force. The medical and personnel planners should take maximum advantage of data presented in the referenced field manuals, but malaria casualty management will tax their abilities to provide functional support.

Medical Units

Medical units are responsible for providing medical support in the theater of operations. Medical planners above division level are responsible for hospitalization, evacuation, medical regulating, medical supply, optical and maintenance, preventive medicine, dental, veterinary, and other functional medical support. Prevention and control of malaria have significant impact on preventive medicine units, evacuation units, and hospitals.

Entomology units are responsible for providing professional and technical personnel for field study, survey, and control of disease vectors and reservoirs and related environmental problems in the area of operation.[53] Inherent in this mission is identification and destruction of mosquito and potential breeding areas, as well as providing advice and assistance to combat field sanitation teams. In many instances, the nature of the combat situation will not allow the preventive medicine mission to be accomplished. During the Sicily Campaign, only one of three malaria units earmarked for Seventh Army arrived in theater. It arrived at D+4 when Seventh Army was moving at a

rate of 10-35 miles per day; very little could be accomplished as an effective malaria control measure.[54] Complete effectiveness of entomology and other preventive medicine units will be challenged even more on the battlefield of the future.

Evacuation units and hospitals in the field will be heavily taxed due to the onslaught of malaria. Utilization of both ground and air evacuation assets to transport malaria casualties will be required to expedite treatment, and hopefully, return to duty status. In the combat zone, air ambulance is the primary means of patient evacuation with life or limb threatening injuries or illnesses. Many of these resources will be diverted for transporting malarial casualties, particularly falciparum malaria casualties. After the patient arrives at the hospital, regardless of evacuation means, comprehensive care is required to facilitate patient return to duty. However, in many cases malarial casualties cannot be returned to duty within the specified theater evacuation policy; they must be evacuated out of the theater of operations. During the Vietnam War, the 6th Convalescent Center was established at Cam Ranh Bay by direction of General William Westmoreland, Commander of U.S. Army, Vietnam, to retain malarial patients in-theater who could not be returned to duty within the 30-day evacuation policy.[55] This action, of course, increased the requirement for medical personnel to staff the center.

The nursing care requirements for malarial patients is well documented by Glor, et. al., during the Vietnam War.[56] In her case study, Glor observed 50 American soldiers, who had contracted malaria, for twenty-one days. The average hospital stay for each patient was 30 days. Clinical nursing rounds for these patients were modified over

traditional rounds to facilitate obtaining research data. To facilitate the research effort, patient illness was divided into phases as follows: first through seventh day - acute phase; eighth through fourteenth day - intermediate phase; and fifteenth day through discharge - recovery phase.

Nursing care requirements were divided into both supportive and therapeutic measures. Supportive measures included personal care such as bathing, oral care, back care, linen exchange, personal hygiene, teaching, counselling, and recreational and occupational therapy; they were controlled by the nurse. Therapeutic nursing measures included administration of prescribed medications and treatments, and prescribed measures dictated by the medical care plan. The sample times taken during the acute phase revealed an average of 3.7 hours and 2.4 hours for therapeutic measures and supportive care measures, respectively.[57]

Even though the sample size in this research was small, the results can be used as an indication of medical care requirements for other falciparum malaria casualties in Vietnam. In Glor's opinion, the two military physicians and three nurses, who assisted her, could not provide continuous 24-hour observation on the patients. This was due to the shortage of personnel and medical and nursing demands of the combat situation.

Personnel Replacements

Providing timely personnel replacements to combat arms units during war is a formidable challenge. If malaria is endemic in the area of operation, the personnel replacement problem is compounded. Combat arms unit commanders need their infantrymen and tank crewmembers hastily

replaced in order to efficiently manage violence on the battlefield. In several wars involving American forces, malaria has caused more casualties than enemy armament.

Field Manual 101-10-1, Staff Officer's Field Manual Organizational, Technical and Logistical Data provides guidance on estimating personnel losses based on the nature of the operation. The personnel planner is responsible for determining the employment of the Personnel and Administration Battalion comparable with the combat situation. The Personnel and Administration Battalion provides command, control, staff planning, and supervision of assigned or attached units that furnish direct support personnel, administrativem replacement and other services to non-divisional troops in the Corps area.[58] Even though casualties resulting from malaria impact on many functions of the Personnel and Administration Battalion, only the function of replacements will be addressed briefly.

The history of the employment of United States Army forces is plagued with personnel replacement problems. The major cause of the problems were due to insufficient replacements available in the resource pool, rather than the operation of the replacement units. During the Korean War, airlift was transporting approximately 340 replacements daily by 5 August 1950. At the same time, 8th Army had sustained 7,859 losses, but only 7,711 individual replacements reached the Far East Command, and only part of them had arrived in Korea.[59] At one point, the personnel picture was so bleak that an urgent request was forwarded to Washington to send 8,000 soldiers to the Far East Command within 15 days. There was an urgent need for infantry and artillery soldiers since all infantry

regiments in Korea were critically short of these specialty soldiers.[60] The request also stipulated that airlift be expanded to accommodate getting 8,000 soldiers in-theater. Personnel shortage was not the only problem encountered by the Far Ear Command, as the decrease in trained replacements created more problems. This problem was recognized by General Douglas MacArthur and he took actions to improve them. On 1 July 1951, he stipulated that all replacements shipped to the Far East Command be qualified and experienced, for they were going directly into combat in Korea for an indefinite period.[61]

In Vietnam a similar, but yet different, personnel replacement picture can be painted. The 9th Division probably had the worst encounter with the personnel replacement system. The division suffered heavy casualties during the Tet battles and post-Tet counteroffensive in the Dinh Trong Province. Since only three rifle companies were assigned per battalion, many rifle companies ended up with 65 or 70 infantrymen present for field duty, rather than 120.[62] It was recognized that no improvement in the 9th Division strength situation would have an adverse effect on combat effectiveness of the unit. The normal personnel reporting system had a built-in lag time of several days, which was compounded during combat conditions.[63] As a result, unit losses due to rotation and battle casualties were not replaced in a timely manner.

Impact On Mission Accomplishment

Noneffectiveness of soldiers due to malaria has had adverse impact on accomplishing their units' missions. Hospital admission statistics from the last three wars involving American forces reveal an alarming

picture. These statistics indicate that for the duration of each war, malaria ranked high as a disease of military significance. As an example, Figure 4 provides data on man-days lost, by cause, among American military personnel during the Vietnam War from 1967 to 1970.[64] Even though the trend reflects a decrease for malaria during the reporting period, it can clearly be deciphered that unit commanders were concerned about the loss of trained soldiers for 21-30 days.

Loss of trained soldiers for long periods of time reduces the effectiveness of units to accomplish their missions. The combat commander undergoes a meticulous decisionmaking process, in most cases, prior to deriving at and approving a plan outlining the course of action. The decisionmaking process directs both the commander and the coordinating staff to make estimates based on the nature of the threat, area of operation, relative combat power, and other factors. As the commander and his staff make estimates in their areas of expertise, they are relying on having the personnel available to execute their envisioned concepts of the operation. It is the personnel or individual soldier who becomes the vehicles by which the commander manages violence on the battlefield. In addition to managing violence on the battlefield, the commander must be able to exploit the weakness of the enemy when the "window of opportunity" opens. The fast-moving modern battlefield, together with the increased lethality of the weaponry, will not allow commanders a second opportunity to exploit a bypassed vulnerability. Consequently, the commander can best accomplish his assigned mission when the unit's strength is at or above the authorized level.

The nature of the modern battlefield, itself, will generate numerous combat and disease nonbattle injury casualties. It is the responsibility of medical assets to return soldiers to duty within the specified combat zone and communications zone evacuation policies. Medical assets are additionally responsible for coordinating evacuation of patients out of the theater of operations, when they can not return to duty within the stated evacuation policy. Soldiers evacuated out of the theater must be replaced in order for units to remain combat effective. Moreover, replacements must be military occupational specialties qualified to reduce further denigration in unit effectiveness. When the number of soldiers killed or wounded due to enemy armament is coupled with the number of malaria casualties evacuated to the rear, the combat commander becomes faced with some critical choices. Even clever commanders have had to delay or withdraw from battles, as stated earlier in this chapter, due to unit endemnicity with malaria.

FIGURE 4. APPROXIMATE NUMBER OF MAN-DAYS LOST FROM DUTY, BY CAUSE, AMONG U.S. ARMY PERSONNEL IN VIETNAM, 1967-70

Preliminary estimates based on sample tabulations of individual medical records.

Cause	1967	1968	1969	1970
Malaria	228,100	215,400	183,050	167,950
Acute respiratory infection	66,800	83,181	63,530	70,800
Skin disease (including dermatophytosis)	66,400	64,832	50,790	80,140
Neuropsychiatric conditions	70,100	106,743	125,280	175,510
Viral Hepatitis	80,700	116,981	86,460	85,840
Diarrheal diseases	55,500	60,132	48,980	45,100
Venereal disease (excluding CRO[1] cases)	7,500	6,840	3,130	3,700
Fever of undetermined origin	205,700	289,700	201,500	205,500
Disease total	780,800	943,809	762,720	834,540
Battle injury and wounds	1,505,200	2,522,820	1,992,580	1,044,750
Other injury	347,100	415,140	374,030	309,670

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ENDNOTES

Chapter Three

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CHAPTER FOUR

PRESENT MALARIA RESEARCH ACTIVITIES

Malaria research activities in the 1980's have undergone a significant change in orientation in the past decade. Prior to 1970 malaria research activities were geared toward vector control and antimalarial drug development. Since these measures were perceived as a means to eradicate the malarial problem, insufficient emphasis was placed on studying the biology of the malarial parasite. The attitude of scientists toward malaria research prior to 1970 is best described by Major General Blumberg, Commanding General, U.S. Army Medical Research and Development Command, in his welcome remarks to the Panel Workshop on Biological Research in Malaria in 1969:

> In recent discussions with Dr. Robert Marston, the Director of the National Institutes of Health, I have come to realize that the U.S. Army carries the brunt of this program for the free world. No other concerted effort is being made since in the United States malaria is not a public health problem. However, when our military is called upon to serve out of the United States, in areas where malaria exists, it becomes an important problem.[1]

The emergence of Anopheles mosquitoes resistant to insecticides and plasmodium resistant to antimalarial drugs mandated a change in orientation on the malaria eradication program. Development of a vaccine for human malaria was perceived as a viable alternative. However, it was realized that insufficient information had been gathered on the biology of the plasmodium organism. Concurrently, research continued on the

development of more effective antimalarial drugs to combat chloroquine-resistant falciparum parasites. Research on both a vaccine for human malaria and new antimalarial drugs is still a necessity, until a vaccine is developed. The interest in malaria vaccine development is increasing.

The renewed interest in developing a vaccine for malaria is because of the removal of some, but not all, obstacles hindering initial progress. The promising results of malaria immunization experiments using suitable laboratory animals have been well documented: Sadun et. al., 1969; Michell et. al., 1977; Siddiqui et. al., 1978; Reese et. al., 1978; and Wellde et. al., 1979.[2] The success of these experiments and the successful cultivation of P. falciparum in vitro (Trager and Gensen, 1976; Haynes et. al., 1976) add new hope to the possibility of developing a vaccine for malaria.[3] As a result of persistant research on the plasmodium organisms, several stages of the plasmodium is being investigated as possible antigens for a malaria vaccine; each developmental stage has unique antigenic determinants.

As mentioned in Chapter Three, the Anopheles mosquito injects sporozoites into the human victim during the blood meal, that rapidly localizes within hepatic parenchymal cells of the host. Each sporozoite develops into thousands of individual merozoites that rupture out of the liver cells and invade erythrocytes. Within the erythrocyte the parasite divides into merozoites, each capable of invading another erythrocyte. Gametocytes are formed from a small percentage of the asexual parasites, which are infectious to mosquitoes for transmission to other victims.[4]

Preclusion of sporozoite entry into or growth within the liver or interruption of asexual erythrocytic development would eliminate malaria

in humans and transmission to the mosquito vector. Even though the individual would not be protected from the consequences of the disease itself, blocking of gametocytic infectivity of mosquitoes would stop transmission of the infection.[5] Malaria can be eliminated by a fully effective vaccine against any of the stages; consequently, three major approaches to vaccine development are being pursued.

The three malaria vaccine candidates are; sporozoite vaccine, blood-stage vaccine, and gametocyte vaccine. The sporozoite vaccine is a live, attenuated vaccine prepared from X-irradiated sporozoites. The sporozoite vaccine prevents infection of the susceptible host, does not require an adjuvant, and is the only malaria vaccine successfully tested in humans.[6] The blood-stage vaccine or merozoite vaccine is a killed vaccine, requires an adjuvant, and is designed to reduce morbidity and/or mortality by eliminating or reducing blood-stage schizogony.[7] The gametocyte vaccine is also a killed vaccine that requires an adjuvant. However, its mode of action is to interrupt malaria transmission by neutralizing gametocytes that have been released from their host cell.[8] The U.S. Army and U.S. Navy are performing research on one or more of the vaccine candidates. In addition, the World Health Organization, through its Special Programs for Research and Training in Tropical Diseases, is conducting research on vaccine development as well as monitoring malaria research and vaccine development programs worldwide.

Army Malaria Vaccine Development

The U.S. Army Medical Research and Development Command (USAMRDC) is the primary Army agency conducting biomedical research. The USAMRDC

was established on 20 August 1958 under the jurisdiction of the Surgeon General at Washington, D.C., by General Order Number 31, Headquarters, Department of the Army, dated 25 August 1958.[9] A dynamic research program is ensured through in-house and contract programs. The technical research program is divided into the five major areas listed below:

Research Area I - Military Disease Hazards Research

Research Area II - Combat Casualty Care

Research Area III - Health Hazards of Military Systems

Research Area IV - Combat Maxillofacial Injury/Combat Dentistry

Research Area V - Medical Defense Against Chemical Agents[10]

Research area managers, in the USAMRDC headquarters, exercise overall planning, management, and coordination of research programs within the research area.[11] The command consists of nine research installations in the Continental United States, and five outside Continental United States facilities. Malaria research is one of the eleven research projects that comes under the auspices of Research Area Manager I.[12]

The Army's malaria research program is spearheaded by the Walter Reed Army Institute of Research (WRAIR), located at the main Walter Reed Army Medical Center, Washington, D.C. The WRAIR was first founded in 1893 as the first preventive medicine school and has always had an associated mission to conduct research in the field of military preventive medicine.[13] The WRAIR pursues a research program which extends from basic research through product development. Goal directed basic research is aimed at understanding the molecular biology of agents causing militarily important diseases such as malaria, hepatitis, and shigellosis, and are complemented by basic studies of immunology and

epidemiology.[14] In addition to the major malaria research that occurs at the WRAIR, malaria research is conducted at the USA Medical Component, Bangkok, Thailand.

Division of Communicable Diseases and Immunology

The Division of Communicable Diseases and Immunology, WRAIR, is responsible for orchestrating the malaria vaccine development research program. The mission of this major subordinate division of WRAIR is to conduct research studies on the etiology, ecology, pathogenesis, diagnosis, prevention and therapy of selected diseases of military importance, and to develop, validate and apply methods of disease control through the use of immunizing agents including studies of the modifications induced in the host by natural or artificial exposure to living, attenuated or killed disease agents.[15] Also, this division provides reference and consultative services on the diagnosis, epidemiology, control and chemotherapy of infectious diseases of military importance in man.[16]

There are three departments in the Division of Communicable Diseases and Immunology associated with malaria research. They are: Department of Immunology, Department of Entomology, and Department of Biologic Research. The Department of Immunology conducts research on the mechanisms of immunity in infectious diseases with present emphasis on malaria, trypanosomiasis, and leishmaniasis.[17] The Department of Entomology conducts laboratory and field investigations (includes physiology, ecology, and biosystematics of vectors of protozoal diseases of man) on arthropods of actual or potential medical importance to the

military.[18] Special emphasis is placed on interrelationships between vector, host, and pathogen with a goal of developing information which can be used to control arthropod-borne diseases. The Department of Biological Research conducts investigations on the development and production of new and/or improved biological products for use in the diagnosis, prevention and treatment of infectious diseases of military importance; and produces pilot scale lots of biologicals for use in research and in human field trials.[19] All departments mentioned play a major role in perpetuating malaria research and vaccine development. However, for the purposes of this thesis, primary emphasis is focused on the malaria vaccine development program of the Department of Immunology.

The Department of Immunology consists of both military and civilian scientists whose areas of expertise include immunology, immunochemistry, parasitology, malariology, entomology, and biology. The diverse backgrounds of avid scientists coupled with dedication to the research effort, are instrumental in perpetuating the vaccine development program.

In addition to dedicated scientists, the Department of Immunology relies on coordination and collaboration to promulgate the malaria vaccine development program. Internal coordination of the vaccine development program with the departments mentioned above and the Division of Medicinal Chemistry are continuous and basically informal.[20] Periodic scientific and technical conferences, review of current technical reports and scientific publications, and personal contact are the mechanisms of coordination. The collaborative effort includes supplementing in-house research with extramural contracts with civilian

institutions, other U.S. government agencies, and the World Health Organization.[21]

The primary focus of the Army malaria vaccine program is development of a vaccine for Falciparum malaria. Research is oriented towards investigations on a blood-stage and sporozoite vaccines. As mentioned in Chapter Two, a sporozoite vaccine using irradiated mosquitoes as innoculators of noninfective sporozoites, has been successful on a few volunteers. However, using irradiated mosquitoes to confer immunity on a large population, such as the Army, is not practical. At the WRAIR, emphasis is placed on developing both a sporozoite and a blood-stage or merozoite vaccine.

Pursuit of a sporozoite vaccine presents many formidable problems. Sporozoites are very hard to obtain in large quantities because they develop only in mosquitoes that have fed on human blood containing mature gametocyte forms of the parasite.[22] In order for a sporozoite vaccine to be effective, the vaccine must kill 100 percent of the sporozoites. If only one sporozoite escapes destruction by a person's immune system and allowed to develop in the liver, the ensuing infection in the bloodstream will be just as severe as in a non-vaccinated individual, since the sporozoite surface antigen does not cross-react with the blood-stage parasite antigen.[23]

The current research efforts on a sporozoite vaccine is showing improvements. Recently, infectious gametocytes have been obtained by the culture method. Other recent advances include the finding that monoclonal hybridoma antibodies to major sporozoite surface antigen can protect mice against mouse malaria.[24] Monoclonal antibodies have also

been made against subhuman private and human malaria sporozoites. Research is directed towards cloning the gene for this sporozoite surface antigen into bacteria using recombinant DNA techniques, and that the bacteria can then be made to produce the antigen in large enough quantities to be useful in developing a vaccine.[25]

The merozoite vaccine development program is still in the early stages. Merozoites are those forms of the parasite which are produced at the final stage of parasite development inside the red blood cell and are then released into the bloodstream where they must find, attach to, and invade new red blood cells to continue the parasite cycle.[26] The successes in immunizing animals against merozoites give credence to the possibility of developing an effective vaccine against this stage of parasite development. Based on observations in humans and experimental data in animals, it can be predicted that: (1) partial protection of an individual by a merozoite vaccine will not only decrease the severity of a malaria attack by decreasing the number of merozoites which successfully invade new red blood cells, but it will also (2) allow the individual to mount relatively rapid and strong secondary antibody and cellular immune responses which would then have a good chance of curing the individual of the infection.[27] Research at the WRAIR has proven that antibodies can block merozoite invasion, and is now oriented on identifying the corresponding antigens on the surface of the merozoite. These antigens are difficult to produce in large amounts from culture largely because of difficulties in growing the parasite. Further research is geared to producing the antigens in bacteria using

recombinant DNA techniques. Extracts of several malaria vaccine development protocols are contained in Appendix A.

Navy Malaria Vaccine Program

The U.S. Navy Medical Research and Development Command (NMRDC) was established on 1 July 1974 at Bethesda, Maryland to manage and coordinate the Navy Medical Department Research, Development, Test, and Evaluation programs concerning the health, safety, and performance effectiveness of Navy and Marine Corps personnel.[28]

The Naval Medical Research Institute (NMRI), subordinate element of the NMRDC, was commissioned in 1942 at Bethesda, Maryland, to conduct Navy medical research in infectious diseases and operational problems. The mission of the NMRI is to conduct research, development, test, and evaluation relevant to the health, safety, and performance of naval personnel, and to perform other functions or tasks directed by the Chief, Bureau of Medicine and Surgery.[29] The NMRI instituted a malaria research program in 1942; the current initiative on malaria vaccine development started in 1974.

The Infectious Diseases Program Center, NMRI, is responsible for monitoring the malaria vaccine development program. The mission of the center is to study host microbial factors important in infectious processes which involve immunological, biochemical, and genetic approaches directed toward development of protective or therapeutic measures against pathogens of relevance to naval personnel.[30]

The Malaria Branch of the Infectious Disease Program Center, is responsible for conducting malaria research relevant to Department of

Defense operations. Development of a vaccine for malaria is the long term goal, and basic studies of parasite antigens and host response to parasite invasion are important areas of experimentation leading toward accomplishing it.[31] The malaria vaccine research and development effort is executed by civilian and military scientists and investigators in the diverse specialties as parasitology, immunology, malariology, chemistry, entomology, and genetic engineering.

The success of the vaccine development program, just as the Army's, depends on collaboration between in-house laboratories, contract laboratories and outside research sources. The majority of the Navy's research is performed in-house, however, a very important aspect of the vaccine development program involves collaboration with civilian universities, such as Michigan State University and the Mahidol University, Bangkok, Thailand.[32] Also, collaboration with other U.S. Government agencies, the World Health Organization and the Instituto De Salubridad Nacional, Bogota, Columbia, is continuous.

One aspect of parasitology research at the Naval Medical Research Institute is directed toward developing an effective vaccine against malaria. The malaria vaccine program is based on radiation-attenuated sporozoites which are immunogens, but require separation from their mosquito host and purification.[33] The sporozoite vaccine development program consists of the following elements: production of the antigen, attenuation of the antigen, purification of the antigen, and development of an assay system for monitoring the immune response to vaccine preparations.[34]

Currently, infecting laboratory mosquitoes and harvesting the sporozoite is the only method of producing antigens for sporozoite vaccine preparation. Since sporozoites are unable to reenter cells to form megacysts which is capable of further development only as exoerythrocytic stages, the in vitro production of sporozoites from precursor stages is not a viable option.[35] Research is directed toward identification and development of a source of gametocytes for infecting mosquitoes. Human volunteers in experimental clinical centers, naturally infected residents of endemic areas, non-human primates, and continuous culture systems of the erythrocytic stages, are sources under consideration.[36]

Attenuation of the sporozoite is required when experimenting with mosquitoes infected with P. falciparum. Even though normal sporozoites are immunogenic, attenuation is necessary to render them non-pathogenic. The accepted method of attenuation is by irradiation of the infected mosquito, although limited protective immunity has been observed in mice vaccinated with freeze-thawed or formalin-treated sporozoites. However, current research with gamma-ray emitters, bilateral cobalt-60 source, to inactivate sporozoites is successful. Investigations on the feasibility of substituting a portable cesium-137 which can be transported to an endemic area for pilot studies apparatus for sporozoite inactivation and preliminary results are encouraging.[37] Also, investigations on the effects of radiation on sporozoites of different ages during their development in the mosquito reveal that mosquitoes irradiated ten days or more after taking an infective blood meal, the sporozoites become

permanently attenuated, but develop normal immunogenicity.[38] The results have practical implications for vaccine production.

The third element in sporozoite vaccine development concerns separation of attenuated sporozoites from mosquito tissues and other contaminates rendering the vaccine unsuitable for use in humans.[39] To dissect the salivary glands of each infected mosquito is impractical and other methods are quite involved. Completed investigations resulted in replacing the linear density gradient with a discontinuous gradient consisting of one light and one heavy layer which concentrate sporozoites at interface upon centrifugation.[40] This modification was an improvement over previous methods since an average of 15,000 sporozoites were recovered; however, experimental animals became sensitized to gradient components after one or two immunizing doses and deaths occurred after three or more doses.[41] Research efforts are underway toward the eventual goal of achieving sterility in the sporozoite preparation. Attempts at characterizing the sporozoite antigens that induce protection are still in the preliminary stages.

Development of an assay to monitor the immune response elicited by candidate vaccine preparations is the last element in producing a sporozoite vaccine. Serology offers the most sensitive test for this purpose and must demonstrate the characteristics necessary for a suitable assay of protection which are specificity, sensitivity, and correlation with protection.[42]

An indirect fluorescent antibody (IFA) test which fulfills all of these criteria has been under development in the vaccine program for the past five years. With the IFA test four classes of antigens have been

identified in sporozoite vaccine preparations: (1) sporozoite specific antigens (2) common antigens shared by other stages of the parasite (3) mosquito antigens (4) and antigenic components introduced during processing.[43] Data is being collected which allows investigators to predict, within limits, the success or failure of a vaccination course in laboratory animals.

Abstracts of several malaria vaccine development protocols are contained in Appendix B.

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Chapter Four

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[19]Ibid., p. 21.

[20]David Huxoll, "Walter Reed Army Institute of Research Program in Malaria," Notes from LTC Huxoll's Office Files, n.d., p. 15.

[21]Ibid., p. 17.

[22]J. David Haynes, Chief, Department of Immunology, Walter Reed Army Institute of Research to Author, 3 December 1982.

[23]Ibid.

[24]Ibid.

[25]Ibid.

[26]Ibid.

[27]Ibid.

[28]U.S. Navy, Navy Medical Research and Development Command Instruction 5450.1A, Organization Manual, January 1982, p. 2.

[29]U.S. Navy, Navy Medical Research Institute Instruction 5400.1N, Organizational Manual, October 1982, p. 1.

[30]Ibid., p. 21.

[31]Ibid.

[32]"Infectious Disease Program Center," Command Historical Report 1981, n.d., p. 43.

[33]"Production of Radiation-Attenuated Vaccines Against Malaria and Schistosomiasis," International Journal of Nuclear Medicine and Biology 7, (1980): 113.

[34]Ibid., 114.

[35]Ibid.

[36]Ibid.

[37]Ibid., p. 115.

[38]Ibid.

[39]Ibid.

[40]Ibid.

[41]Ibid.

[42]Ibid., p. 117.

[43]Ibid.

CHAPTER FIVE

SUMMARY/CONCLUSIONS/RECOMMENDATIONS

Summary

The history of the United States Army is replete with the devastating effects of malaria on combat effectiveness. Malaria has been a major cause of manpower loss in the theater of operations during two general wars as well as two limited wars. Considering an average loss of 30 days per case of malaria and the relapsing effect of the disease, malaria boasts the highest disease incidence rate for all of the last four wars - except the Korean War.

Malaria was manifesting its devastating effects on warring armies and the civilian populace centuries prior to isolating the causative agent and the vector transmitter. Early belief that malaria was caused by inhaling bad air from stagnant water sources was dispelled by the French military physician, Charles Laveran. In 1880 he discovered plasmodium, a protozoan, as the parasite causing malaria. Even though the mosquito was associated with malaria for centuries, it was not until 1898 that the genus Anopheles was proven to be the vector transmitters of bird malaria by the Indian physician, Ronald Ross. Anopheles was confirmed as the vector transmitter of human malaria shortly afterwards. Malaria was a major cause of death in many countries of the world at the time of

these historic discoveries. Warring armies invading these countries were by no means spared of this dreadful disease.

The American military used a three-prong approach in establishing a malaria prophylaxis program. Antimalarial drugs were used as a suppressive drug to prevent malaria and as a therapeutic agent to treat soldiers who had contracted malaria. The efficacy of the antimalarial drugs has been continuously challenged since World War I. Consequently, research has been conducted, although on a sporadic basis, to improve antimalarial drugs. To initiate research on an improved antimalarial drug, prior research had to be completed and an in-depth knowledge acquired on the plasmodium organism. As a result of the research on the plasmodium (and in some cases the vector mosquito) and antimalarial drug development, the following drugs were used as an antimalarial prophylaxis during the last four wars:

World War I - Quinine

World War II - Quinine; Quinicrine; Atrabrine; Meprocrine

Korean War - Chloroquine

Vietnam War - Chloroquine - primaquine

Chloroquine - primaquine - dapsone

Chloroquine - primaquine - DDS (4,-4'-diamino -diphenylsulfone)

The mobilization of the industrial base during World War II afforded massive and intensive antimalarial drug research programs by medical preparedness planners. The pinnacle of the research endeavor was the discovery of the antimalarial properties of quinicrine, and later chloroquine in 1943. Since that time, chloroquine has been the drug of choice

to prevent malaria during miltary operations. However, soldier discipline problems were encountered during all four wars with the administration of antimalarial drugs. In addition to the soldier discipline problems in Vietnam, the malaria prevention program was exacerbated by the discovery of plasmodium strains resistant to chloroquine. Chloroquine-resistant strains of plasmodium are also found in Africa and Latin America, and is a major contributor to the worldwide resurgence of malaria.

A seccnd antimalarial preventive measure is environmental controls. Prior to the confirmation, by Ronald Ross in 1897, that mosquitoes were vectors transmitting malaria, the deepseated belief that draining stagnant water areas influenced the reduction in incidence of malaria prevailed. The favorable results obtained by drainage led to other environmental control measures. Ditching, dredging, filling in open areas, and dispensing insecticides and petroleum products on mosquito breeding areas were effective in controlling and eliminating the mosquito populations. However, these control measures were restrictive, although effective. The discovery of Paris green as a larvacide added much improvement to the mosquito control program, but it was the discovery of DDT (dichlorodiphenyltrichloroethane) that gave renewed impetus to the program.

Dichlorodiphenyltrichloroethane (DDT) was discovered in 1943 as a result of intensified efforts to discover a larvacide more effective than Paris green. The fact that DDT would not only kill mosquito larvae, but adult mosquitoes, gave credence to possibility of eradicating malaria. The most amazing property of DDT, however, was its residual effect. The

insecticide remained lethal for three months after application, thereby reducing significantly the requirement for repeated administrations. Airplanes were modified during World War II to allow disperal of DDT over swampy areas that were inaccessible by ground transportation vehicles. The effectiveness of dispensing DDT as a mosquito control measure in many areas of the world is unparalleled. However, mosquitoes resistant to DDT have been discovered in many countries of the world; this factor contributes to the worldwide resurgence of malaria.

The final approach to reducing the incidence of malaria among soldiers is complying with individual protective measures. Individual protective measures can be instituted by the soldier while he is at work or at rest. These measures include proper wear of the uniform, correct use of protective nets and screening devices, proper use of insect repellents, and compliance with other established malaria control measures. Soldier discipline problems result from lack of compliance with individual protective measures and therefore require command emphasis, to include reeducation, at all levels of command to enforce this significant problem.

The three-prong approach to preventing malaria has been partially successful. The success achieved however, is noteworthy since failure in reduction of the malaria incidence in deployed areas could have resulted in mission failure. Considering Army force modernization, United States interests, and conceivable threats to those interests, impediments to mission accomplishment of deploying forces, once identified, should be eliminated.

The United States has varied interests in many areas of the world. They fall into the broad categories of political, economic, military, and strategic. Though the chances of direct confrontation with the Soviet Union to protect these interests are almost nil, confrontation with Soviet Union surrogates and proxies in areas of vital interests are highly probable. A decision by the National Command authority could result in deployment of the Rapid Deployment Force to protect interests of the United States. The current instability in both Somalia and El Salvador could result in deployment of American forces to Africa and Latin America respectively. The ability to conduct sustained operations in these areas will depend, in part, on how well we can cope with the problem of malaria. Malaria is resurging in both areas due to the resistance of plasmodium to antimalarial drugs, resistance of anopheles vectors to insecticides, and the governmental attitudes toward the malaria eradication program. Since there has been no mosquito transmitted malaria case in the United States since 1974, the military has an interest in the current resurgence of malaria worldwide. Development of a vaccine for malaria will provide permanent protection in endemic areas. The civilian industry has not demonstrated an equal interest in antimalarial vaccine development because their product would not be marketable and profit making in the United States unless a war started. Consequently, there is a need for the military to conduct research on a vaccine for malaria.

Malaria vaccine development programs are conducted by both the U.S. Army and the U.S. Navy. The primary focus of the Army's vaccine program is development of a sporozoite and a blood-stage or merozoite

vaccine. This research effort is conducted by the Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research (WRAIR), a subordinate unit of the U.S. Army Medical Research and Development Command. In addition, the WRAIR has a subordinate unit in Bangkok, Thailand, supplementing the vaccine development program. The Navy's vaccine program is oriented toward development of a sporozoite vaccine. The Naval Medical Research Institute, a subordinate of the Navy Research and Development Command, conducts the vaccine development research.

The malaria vaccine development programs, of both services, require extensive coordination and collaboration. Investigations on vaccine development are performed by civilian and military scientists of varied specialities. Institutes of both services conduct in-house research and contract a portion of the research proposals to civilian institutions. The research initiatives of the Army and Navy complement each other and should expedite development of a malarial vaccine.

The complexity of the plasmodium organism is being thoroughly investigated by researchers participating in the vaccine development program. Malaria research prior to the 1960's was oriented toward development of efficacious antimalarial drugs; therefore, limited research was conducted on the biology of the plasmodium. Researchers are bridging the gap on investigating the biology of the plasmodium as they pursue development of a malaria vaccine. In retrospect, however, it was thought that antimalarial drugs and environmental control measures coupled with individual protective measures, would eradicate malaria. There were no prognostications that resistance to antimalarial drugs by

the plasmodium nor resistance to insecticides by mosquito vectors, would occur. These two facts are responsible for the worldwide resurgence of malaria; they caused the breakdown in the World Health Organization's worldwide malaria eradication programs.

Conclusions

The focus of this thesis has been to establish a military need for research and development on a vaccine for malaria. Malaria is only one of the many diseases that has plagued the United States Army as well as other armies throughout history. During several wars, accomplishing the mission was either seriously impaired or ended in failure because of soldiers suffering from the debilitating effects of malaria. Antimalaria prophylaxis measures were established to control malaria, but they were only partially successful.

Research and development endeavors during World War II to improve the antimalarial drug, quinine, and mosquito insecticide, Paris green, gave renewed impetus to the malaria eradication program. However, the discovery of the new antimalarial drug, quinicrine, and later chloroquine, as well as the new insecticide, dichlorodiphenotrichloroethene (DDT), did not occur in time to significantly reduce malaria casualties. Since World War II, research efforts have been directed toward development of more effective antimalarial drugs. The consensus of scientists that antimalarial drugs and environmental control measures would eradicate malaria was a gross miscalculation. In fact, the World Health Organization instituted a worldwide malaria eradication program in 1957. The program was successful in many areas of the world, but not in Africa,

Latin America, and Southeast Asia. In Vietnam, American forces suffered approximately 40,000 casualties from malaria. Malaria is flourishing in areas where it was never eradicated (Africa, Latin America) and resurging in many areas where it was once thought eradicated (Turkey, India).

Several reasons are given for the worldwide resurgence of malaria. The high vectoral efficiency of the anopheles mosquito with its documented resistance to insecticides as well as the innate ability of the plasmodia to resist antimalarial drugs are major contributors to the resurgence of malaria. Other reasons given include inacessability to large population groups due to climatic and topographical factors, lack of fund commitment by the governments in some countries, and the impecunious state of several countries. Hence, countries in Africa and Latin America will continue to experience excessive suffering and death due to contracting malaria.

The United States has interests in both Africa and Latin America. They include economic, political, military and strategic interests which are in jeopardy due to instability in several areas. Protection of these interests are vital to the national goals of the United States, and could result in deployment of American forces. The ability of the Rapid Deployment Force to conduct sustained operations in either Africa or Latin America will be affected by malaria. Force modernization and the sophistication of weaponry on the next battlefield will result in a short war. The ability of combat arms units to acquire targets rapidly and decisively will influence the outcome of many battles. Since malaria is primarily a disease of combat arms units, loss of the vital services of

trained infantrymen and crews, because of malaria, will impair accomplishing the mission. Combat arms soldiers will not be able to effectively institute malaria prophylaxis in the forward areas; therefore, they need permanent protection against the malarial parasite.

Active immunizations against malaria is the best method of conferring permanent protection in soldiers. To date, no active immunization against malaria is available. Three types of malarial vaccines are in various stages of investigation at military research institutes. They are sporozoite, merozoite, and gametocyte; each may be able to confer protection against malaria based on recent studies, using animal models. Of the three vaccine candidates, only the sporozoite vaccine has been tested in humans. Even though the vaccine was successful during testing, the method of conferring immunity with irradiated mosquitoes, is not practical for mass immunizations. Therefore, research should continue in pursuit of an active vaccine against malaria.

Recommendations

1. That the malaria vaccine development program be elevated in priority on the list of projects included in the Department of Defense Research, Development, Test and Evaluation Program. This action should expedite the development of the vaccine and prevent the threat of contracting malaria on the next battlefield.

2. That sufficient funds be appropriated by the Congress to pursue the vaccine development program with vigor. Current budgetary constraints have negatively impacted on the vaccine development program and will probably continue in the future. It is paramount that the funds

identified by the Army and the Navy to support the malaria vaccine development programs in the United States and overseas laboratories are appropriated by Congress.

3. That collaboration and coordination continue between personnel associated with the military malaria vaccine development programs, the World Health Organization and other national and international agencies. The information gained from these associations is invaluable, and prevents duplication of the research effort. The significance of collaboration and coordination of malaria research was realized during World War II when it led to discoveries of both an improved antimalarial drug and an improved mosquito insecticide.

4. That a cost effectiveness analysis be conducted which compares the cost of soldier noneffectiveness time, cost of support requirements for a malaria casualty, and cost of past malaria research, with the cost of the current malaria vaccine development programs. The cost of the current vaccine development programs should include a prediction on the yearly future costs of the program as well as an estimate of the number of malaria casualties that will not occur due to development of the vaccine. While this endeavor will involve intensive research and the assistance of a computer, the results will be invaluable.

APPENDIX A

Walter Reed Army Institute of Research Work Unit Number 098

Title of Research Protocol: Immunology of Plasmodium falciparum in Vitro

Principle Investigator(s): Diggs, Carter L.

Haynes, J.D.

Chulay, H.

Objective: To exploit newly developed methods of culture of human malaria parasites (Plasmodium falciparum) in order to elucidate the mechanisms of immunity to the organism and explore the feasibility of developing a vaccine against this major military infectious disease problem.

Synopsis: The approach is to improve existing culture technology to produce parasite antigens; to characterize these antigens and evaluate them as vaccine candidates by immunizing experimental animals; and to develop in vitro test which are productive of protective immunity.

Results: Tritiated hypoxanthine is avidly incorporated into P. falciparum grown in vitro. Radioisotope incorporation gives results comparable to morphological assessment of growth but markedly increases the number of variables which can be conveniently studied. Factors influencing the amount of incorporation include parasite concentration, erythrocyte concentration, parasite stage, the use exposure to the radioisotope, and the presence of other purines in the culture medium. The methods for the enhanced production of the mature forms of the parasite through culture synchonization were improved.

Source: "Immunology of Plasmodium falciparum in vitro", DD Form 1498, Research and Technology Work Unit Summary, Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, 1 October 1979.

Walter Reed Army Institute of Research Work Unit Number 098

Title of Research Protocol: Immunology of Plasmodium falciparum in Vitro

Principle Investigator(s): Diggs, Carter L.

Haynes, J.D.

Chulay, H.

Objective: To exploit newly developed methods of culture of human malaria parasites (Plasmodium falciparum) in order to elucidate the mechanisms of immunity and explore the feasibility of developing a vaccine against this major military infectious problem.

Synopsis: The approach is to improve culture technology to produce parasite antigens; to characterize these and evaluate them as vaccine candidates in experimental animals; and to develop in vitro tests which are predictive of protective immunity.

Results: Current work is based on methods for the continuous culture of P. falciparum simultaneously developed at the WRAIR and at the Rockefeller University. Methods for synchonizing the growth of the parasite have been improved and small amounts of merozoites have been obtained from culture.

Source: "Immunology of Plasmodium falciparum in vitro", DD Form 1498, Research and Technology Work Unit Summary, Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, 30 September 1980.

Walter Reed Army Institute of Research Work Unit Number 208

Title of Research Protocol: Immunity in Protozoan Diseases

Principle Investigator(s): Hockmeyer, W.T.

Haynes, J.D.

Williams, J.S.

Objective: To conduct immunological studies of protozoan diseases with emphasis on malaria, to produce P. falciparum malaria antigens by in vitro techniques for immunoassay and immunochemical analysis. These studies will aid in the development of a vaccine to protect soldiers stationed in many areas of the world against a major military disease.

Synopsis: The approach is to study, in both animal models and through the use of in vitro techniques, the response elicited by the immune system, to determine the role of cellular and molecular mediators in these processes and to design experimental immunogens which will provide the basis for future vaccine development programs.

Results: Development of a method for lightly fixing merozoites released from synchronized Plasmodium falciparum cultures and attaching these intact merozoites to the bottoms of microtite plate wells for use as the antigen in an enzyme linked immunoabsorbant assay to detect immune antibody directed against the merozoite surface. The importance of non-antibody aspects of protective immunity have been surfaced by the discovery that the growth of parasites can be inhibited by a heat-labile complement dependent factor, and a heat-stabile "tumor necrosis factor".

Source: "Immunity in Protozoan Diseases," DD Form 1498, Research and Technology Work Unit Summary Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, 1 October 1981.

APPENDIX B

Naval Medical Research and Development Command Work Unit Number MR041.05.01.0041

Title of Research Protocol: Effect on Route of Mycobacterium bovis BCG Administration on Induction of Suppression of Sporozoite Immunity in Rodent Malaria.

Principle Investigator(s): Smrkovski, Lloyd L.

Synopsis: Intravenous immunization of mice with 16,000 sporozoites attenuated by ^{60}co-gamma-irradiation produced solid immunity to sporozoite-induced malaria when the mice were challenged 21 days after immunization.

Objective: To determine the influence of the ropute of BCG inoculation on the immune response to sporozoite vaccination.

Results: The study clearly demonstrated that a mycobacterial injection in mice, induced by BCG vaccination, severly alters their protective immune response to sporozoite vaccine. The degree of suppression of immunity is dependent on the route of BCG inoculation and upon the sequence of administration of the two vaccines. BCG vaccine is used worldwide for prophylaxis against tuberculosis, and since mycobacterial infections and diseases are cosmopolitan, the significance of these findings becomes more relevant. In addition, these results suggest a potential for multiple vaccine interference which is obviously inportant. Relationships between vaccines and multiple injections are deserving of special attention.

Source: "Effect of Route of Mycobacterium bovis BCG Administration on Introduction of Suppression of Sporozoite Immunity in Rodent Malaria", Infection and Immunity, (January 1981): 408-412.

Naval Medical Research and Development Command, Work Unit Number MR041.05.01.0068

Title of Research Protocol: Production of Monoclonal Antibodies by Hybridomas Sensitized to Sporozoites of Plasmodium Berghei

Principle Investigator(s):

Synopsis: Hybridoma cell lines, which secreted antibodies directed against either the surface of Plasmodium berghei sporozoites or mosquito debris, were produced by fusion of spleen cells of P. berghei sporozoite immuned mice with P 31-X63-Ag8 myleoma cells. Four cloned antibody-secreting cell lines were successfully established.

Objective: To produce additional hybridomas, to be used for generating monoclonal antibodies against sporozoite antigens in an effort to identify and characterize other antigens that may be important in the irradated vaccine model.

Results: Hybridoma colonies grew in 341 of 1,176 microtiter wells seeded from the spleen cell-mycloma fusion, performed after immunizing the mice twice with irradiated sporozoites. In addition to hybridoma cells that produced antibodies against the sporozoite surface, certain cell colonies demonstrated antibody production against mosquito debris, as detected by indirect immunofluorescent antibody test. This study demonstrated that it is possible to produce and maintain a significant number of hybridoma cell lines that produce antibodies apparently directed toward surface antigens of air-dried, glutaraldehude-fixed, or viable P. beghei sporozoites.

Source: "Production of Monoclonal Antibodies by Hybridomas Sensitized to Sporozoites of Plasmodium Berchei" Journal of Parasitology 68 (December 1982): 1029-1033.

Naval Medical Research and Development Command Work Unit Number MR041.05.01.0041

Title of Research Protocol: Kinetics of Immunosuppression of Sporozoite-Induced Immunity by Mycobacterium bovis BCG.

Principle Investigator(s): Smrkovski, Lloyd L.

Synopsis: Data reported in this study demonstrate that the vaccination of National Institute of Health/Naval Medical Research Institute mice with viable Mycobacterium boris BCG organisms induces a state of immunosuppression that renders the recipient animal incapable of a protective response to the malaria sporozoite vaccine. The expression of this altered protective immune response is dependent upon the dosage of the two live vaccines, as well as upon the sequence of their administration.

Objectives:

(1) To determine whether the BCG-induced suppression of sporozoite immunity is dependent on the number of viable units of BCG administered.

(2) To determine whether the immunosuppression could be overcome by increasing the dose of irradiated sporozoites or the number of malaria vaccinations administered.

(3) To determine whether the in vitro skin test response to tubercle antigens might correlate with suppression.

Results: In previously published reports, it was noted that the inoculation of mice with 10^7 viable units of BCG (Phipps) resulted in an abrogation of their protective immune response to vaccination with

irradiation-attenuated sporozoites. Even though the experiments outlined herein were not specifically designed to determine the precise mechanism(s) responsible for the suppression phenomena, the data do permit a better understanding of the parameters which allow for their expression. The data further suggest that some possible mechanisms, heretofore not considered, may or may not be operative. The data from the BCG dose studies may have relevance in sporozoite vaccine programs involving humans.

Source: Kinetics of Immunosuppression of Sporozoite-Induced Immunity by Mycobacterium bovis BCG, Infection and Immunology 37 (September 1982): 1021-1027.

Naval Research and Development Command, Research Work Unit ZF58.524.009.0068; and Research Grant RR07143 from the U.S. Department of Health and Human Services

Principle Investigator(s): Beaudoin, Richard L. and Pacheco, Nancy D., Naval Medical Research Institute; Mezzoely, Charles A.M., Northeastern University; Erbe, Eric F. and Steere, Russell L., U.S. Department of Agriculture.

Title of Research Protocol: Plasmodium berghei: Architectural Analysis by Freeze-Fracturing of the Intraoocyst Sporozoite's Pellicular System.

Synopsis: The technique of freeze-fracturing has been used to study the architecture of the pellicular complex of the intraoocyst sporozoite of Plasmodium berghei. The sporozoite is surrounded by three plasma membranes and a layer of subpellicular microtubles. During freeze-fracturing, each of the three membranes can split along its hydrophobic interior to yield a total of six fracture faces; each face has globular intramembraneous particles. Two of the fracture faces exhibit a unique arrangement of particles in well-organized parallel rows above the long axis of the sporozoite. This arrangement has not been reported in either the erythocytic or the exoerythrocytic forms of Plasmodium supporatives. Another unique feature in the sporozoite revealed through freeze-fracturing is a single suture line that traverses the long axis of the inner two membranes of the parasite.

Objective: To describe the surface architecture of fractured faces in the pellicular complex of the developing sporozoites of P. berghei in mature oocysts on the midgut of Anopheles stephensi.

Results: The architecture of the pellicular complex of the malaria sporozoite as revealed by freeze-fracture appears to be a unique and persistent feature of that stage of the life cycle of the parasite. The findings suggest that the pellicular complex of the sporozoite does not undergo any discernible morphological change during maturation, which is interesting in view of the difference in immunogenicity observed between oocyst and salivary gland sporozoites.

Source: "Plasmodium berghei: Architectural Analysis by Freeze-Fracturing of the Intraoocyst Sporozoite's Pellicular System" Experimental Parasitology 53 (April 1982): 229-241.

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GLOSSARY

Active immunity -	Disease resistance in an individual due to antibody production after exposure to a microbial antigen following disease, inapparent infection or inoculation.
Adjuvant -	A material that enhances the action of a drug or antigen.
Aliquot -	Dividing a number or quantity without leaving a remainder.
Anemia -	A condition marked by significant decreases in hemoglobin concentration and in the number of circulating red blood cells.
Anopheles -	A genus of mosquitoes in the family Culicidae.
Anopheline -	Pertaining to mosquitoes of the genus Anopheles or a closely related genus.
Antibody -	A protein, found principally in blood serum, originating either normally or in response to an antigen and characterized by a specific reactivity with its complementary antigen. Also known as immune body.
Antigen -	A substance which reacts with the products of specified humoral or cellular immunity, even those induced by related heterological immunogens.
Attenuated vaccine -	A suspension of weakened bacteria, viruses, or fractions thereof used to produce active immunity.
Attenuation -	Weakening or reduction of the virulence of a microorganism.
DDT -	Dichlorodiphenyltrichloroethane; common name for an insecticide.
Endemic -	Peculiar to a certain region, specifically referring to a disease which occurs more or less constantly in a certain locality.
Epidemic -	A sudden increase in the incidence rate of a disease to a value above normal, affecting large numbers of people and spread over a wide area.

Erythrocytes -	Red blood cells.
Eukaryote -	A cell with a definitive nucleus.
Fluorescent antibody test -	A clinical laboratory test based on the antigen used in the diagnosis of syphilis and lupus erythematosus and for identification of certain bacteria and fungi, including the tubercle bacillus.
Gamete -	A mature germ cell.
Gametocyte -	An undifferentiated cell from which gametes are produced.
Heterologus -	Having a different relation; not corresponding, (of cells and antiserums) immunologically related but not identical.
Immunogen -	A substance which stimulate production of specific antibody or of cellular immunity, and which can react with these products.
In vito -	Pertaining to a biological reaction taking place in a living cell or organism.
In vitro -	Pertaining to a biological reaction taking place in an artificial apparatus.
Killed vaccine -	A suspension of killed microorganisms used as antigens to produce immunity.
Malaria -	A tropical disease characterized by high fever, severe chills, enlargement of the liver, and anemia.
Merozoites -	An ameboid trophozoite in some sporozoans produced from a schizont by schizogony.
Parasitemias -	The presence of parasites in the blood.
Paris green -	A poisonous, emerald-green powder used as a pigment and in making sprays for killing insects.
Passive immunity -	Immunity acquired by injection of antibodies in another individual or in an animal.
Plasmodium -	A genus of protozoans in the family Plasmodiidae in which all the true malarial parasites are placed.
Protozoa -	A diverse phylum of eukaryotic microorganisms.

Recrudescences -	A breaking out afresh; renewed activities.
Schizont -	A multinucleate cell in certain members of the Sporozoa that is produced from a trophozoite in a cell of the host, and that segments into merozoites.
Schizogony -	Asexual reproduction by multiple fission of a trophozoite.
Sporozoa -	A subphylum of parasitic Protozoa, typically producing spores during the asexual stages of the life cycle.
Sporozoite -	A motile, infective stage of certain sporozoans, which is the result of sexual reproduction and which gives rise to an asexual cycle in the new host.
Trophozoite -	A sporozoan during its growing stage.

INITIAL DISTRIBUTION LIST

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   U.S. Army Medical Research and Development Command
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9. Lieutenant Commander Lloyd Smrkovski
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U.S. Army Research and Development Command
Fort Detrick, Maryland 21701

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U.S. Army Medical Department Activity
Fort Leavenworth, Kansas 66027